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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent Re. 34,878
Issued: March 14, 1995
To: Shigeshi Toyoshima, Yoshiko Seto, Hisashi Shinkai, Koji Toi and Izumi Kamashiro
For: HYPOGLYCEMIC AGENT

Box Patent Extension
Assistant Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL LETTER FOR PATENT TERM EXTENSION APPLICATION

Sir:

Attached in duplicate is an Application for the extension of the term of U.S. Patent No. Re. 34,878 under 35 USC § 156.

The Commissioner is hereby authorized to charge the $1,120 fee prescribed in 37 CFR § 1.20(j)(1), as well as any additional fees which may be necessitated in connection with the filing of this Application for Patent Extension to Deposit Account No. 19-0134 in the name of Novartis Corporation. Two additional copies of this transmittal letter are being submitted for charging papers.

Respectfully submitted,

Gregory D. Ferraro
Agent for Applicant
Reg. No. 36,134

Novartis Pharmaceuticals Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6923

GDF:

Attachs.: Application for Patent Extension (incl. Appendices A-F) (2)
Two additional copies of this transmittal letter
Postcard

Date: February 13, 2001

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EL138342685US
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent Re. 34,878

Issued: March 14, 1995

To: Shigeshi Toyoshima, Yoshiko Seto, Hisashi Shinkai, Koji Toi and Izumi Kamashiro

For: HYPOGLYCEMIC AGENT

Box Patent Extension
Assistant Commissioner for Patents
Washington, D.C. 20231

PATENT TERM EXTENSION APPLICATION UNDER 37 USC § 156

Sir:

I. Applicant, Ajinomoto Co., Inc., a company organized and existing under the laws of Japan, represents that it is the owner of the entire title and interest in and to U.S. Patent No. Re. 34,878 (reissued from U.S. Patent No. 4,816,484 which issued on March 28, 1989) which was granted on March 14, 1995 to Shigeshi Toyoshima, Yoshiko Seto, Hisashi Shinkai, Koji Toi and Izumi Kamashiro for "HYPOGLYCEMIC AGENT" by virtue of an assignment in favor of:

> Ajinomoto Co., Inc. from and by Shigeshi Toyoshima, Yoshiko Seto, Hisashi Shinkai, Koji Toi and Izumi Kamashiro recorded in the United States Patent and Trademark Office on November 1, 1988 at Reel 4982, Frame 0100.

By the Power of Attorney attached hereto as "Appendix A", Applicant appoints Novartis Corporation, a New York Corporation and a subsidiary and affiliate of Novartis AG, the exclusive licensee of U.S. Patent No. Re. 34,878, as its agent to act in its interest in this matter, and also appoints the attorneys and agents associated with Customer No. 001095, respectively and individually, with regard to this application for extension of the term of U.S. Patent No. Re. 34,878 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

II. Applicant submits this Application for Extension of Patent Term under 35 USC §156 by providing the following information as required by 37 CFR §1.710 through 1.785, especially 1.740.

1. Identification of the Approved Product under 37 CFR §1.740(a)(1)

The complete identification of the approved product is:

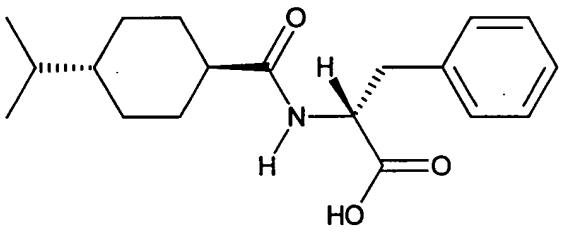
chemical name: N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine

also known as: A-4166; SDZ DJN 608

Tradename: STARLIX®

generic name: Nateglinide

chemical structure:



2. Identification of the Federal Statute under which Regulatory Review Occurred under 37 CFR §1.740(a)(2)

The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act Section 505 (21 USC §355).

3. The Date of Permission for Commercial Marketing under 37 CFR §1.740(a)(3)

The approved product received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act (21 USC §355) on December 22, 2000.

4. Active Ingredient Statement under 37 CFR §1.740(a)(4)

The sole active ingredient in STARLIX® is nateglinide; and nateglinide, or any other pharmacologically acceptable salt thereof, has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act section 505 (21 USC § 355) prior to the approval of NDA 21-204 by the United States Food and Drug Administration on December 22, 2000.

5. Statement of Timely Filing under 37 CFR §1.740(a)(5)

This Application for Extension of the term of U.S. Patent No. Re. 34,878 under 35 USC §156 is being submitted within the permitted 60 day period set forth in 37 CFR §1.720(f), which period will expire on February 20, 2001.

6. Identification of Patent for which Extension is Sought under 37 CFR §1.740(a)(6)

The patent, the term of which this Application seeks to extend, is: U.S. Patent No. Re. 34,878 which issued on March 14, 1995 to Shigeshi Toyoshima, Yoshiko Seto, Hisashi Shinkai, Koji Toi and Izumi Kamashiro, the term of which would otherwise expire on March 28, 2006.

7. Patent Copies under 37 CFR §1.740(a)(7)

A complete copy of U.S. Patent No. Re. 34,878, identified in paragraph 6 above, is attached as "Appendix B".

8. Post Issuance Activity Statement under 37 CFR §1.740(a)(8)

No Terminal Disclaimer, Re-Examination Certificate or Re-Issue has been issued or requested with respect to U.S. Patent No. Re. 34,878. A Certificate of Correction was issued on May 13, 1995 and a copy thereof is attached hereto as "Appendix C". Three maintenance fees have become due since the patent has issued and all three have been paid in a timely manner. A copy of all three maintenance fee statements received by the United States Patent & Trademark Office indicating that the respective maintenance fees were timely paid, including the third Maintenance Fee in the amount of $2910.00, are attached hereto as "Appendix D".

9. Statement Showing How the Claims of the Patent for which Extension is Sought Cover the Approved Product under 37 CFR §1.740(a)(9)

The claims of U.S. Patent No. Re. 34,878 cover certain D-phenylalanine derivatives, per se.

Claim 1 of U.S. Patent No. Re. 34,878 reads as follows:

1. A D-phenylalanine derivative of the formula

$R^4 - CO - NR^3 - CH(COOR^1) - CH_2 - C_6H_5$

or a salt thereof or a precursor which can be converted into said D-phenylalanine derivative in vivo, wherein:

R^1 is hydrogen or C_{1-5} alkyl,

R^3 is hydrogen or C_{1-5} alkyl; and

R^4 is cyclohexane substituted at the 4- or 5-position by methyl, ethyl, isopropyl, tert-butyl, ethene, or isopropene or cyclohexene substituted at the 4- or 5-position by methyl, ethyl, isopropyl, tert-butyl, ethene, or isopropene.

Since the approved product STARLIX® is the D-phenylalanine compound of claim 1, wherein R^1 is hydrogen, R^3 is hydrogen and R^4 is cyclohexane substituted at the 4-position by isopropyl and the substituents on the cyclohexane ring are trans to each other, this claim covers the approved product STARLIX®.

Claim 4 of U.S. Patent No. Re. 34,878 reads as follows:

4. The D-phenylalanine derivative of claim 1, wherein the said derivative is N-(4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

Since the approved product STARLIX® is the D-phenylalanine compound of claim 1, wherein the substituents on the cyclohexane ring are trans to each other, this claim covers the approved product STARLIX®.

Claim 6 of U.S. Patent No. Re. 34,878 reads as follows:

6. The D-phenylalanine derivative of claim 1, wherein the said derivative is N-[(s)-perilloyl]-D-phenylalanine; N-(trans-4-methylcyclohexylcarbonyl)-D-phenylalanine; N-(trans-4-ethylcyclohexylcarbonyl)-D-phenylalanine; N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine; or N-(trans-4-t-butylcyclohexylcarbonyl)-D-phenylalanine.

Since this claim covers the compound N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine, this claim covers the approved product STARLIX®.

Claim 16 of U.S. Patent No. Re. 34,878 reads as follows:

16. The compound N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

Since this claim covers the compound N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine, this claim covers the approved product STARLIX®.

10. Statement of Relevant Dates to Determine the Regulatory Review Period under 37 CFR §1.740(a)(10)

The relevant dates and information pursuant to 35 USC §156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

a) An Investigational New Drug Application for nateglinide was submitted to Department of Health and Human Services on February 6, 1995 and received by the Department of Health and Human Services on February 7, 1995 and the IND number assigned was 47,235.

b) A New Drug Application was submitted to and received by the Department of Health and Human Services on December 17, 1999 and the NDA number assigned was 21-204.

c) The date on which NDA 21-204 was approved was December 22, 2000.

11. Brief Description of Activities Undertaken During the Regulatory Review Period under 37 CFR §1.740(a)(11)

As a brief description of the activities undertaken during the applicable regulatory review period, attached hereto as "Appendix E" is a chronology of the major communications between the US Food and Drug Administration and the Applicant in the IND and NDA mentioned in paragraph 10 above.

12. Opinion of Eligibility for Extension under 37 CFR §1.740(a)(12)

Applicant is of the opinion that U.S. Patent No. Re. 34,878 is eligible for extension under 35 USC §156 and 37 CFR §1.720 because it satisfies all of the requirements for such extension as follows:

(a) 35 USC §156(a) and 37 CFR §1.720(a)

U.S. Patent No. Re. 34,878 claims a human drug product, nateglinide.

(b) 35 USC §156(a)(1) and 37 CFR §1.720(g)

The term of U.S. Patent No. Re. 34,878 (expiring March 28, 2006) has not expired before the submission of this application.

(c) 35 USC §156(a)(2) and 37 CFR §1.720(b)

The term of U.S. Patent No. Re. 34,878 has never been extended.

(d) 35 USC §156(a)(3) and 37 CFR §1.720(c)

The Application for extension of the term of U.S. Patent No. Re. 34,878 is submitted by the authorized agent of the owner of record thereof in accordance with the requirements of 35 USC §156(d) and 37 CFR §1.740.

(e) 35 USC §156(a)(4) and 37 CFR §1.720(d)

The approved product, STARLIX®, has been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 USC §156(a)(5)(A) and 37 CFR §1.720(h)

No other patent has been extended for the same regulatory review period for the approved product, STARLIX®.

13. Length of Extension Claimed Under 37 CFR §1.740(a)(12)

The length of extension of the patent term of U.S. Patent No. Re. 34,878 requested by Applicant is **1259** days, which length was calculated in accordance with 37 CFR §1.775 as follows:

(a) The regulatory review period under 35 USC §156(g)(1)(B) began on February 6, 1995 (the filing date of the IND) and ended on December 22, 2000,

amounting to a total of 2,146 days or 5.88 years, which is the sum of (i) and (ii) below:

(i) The period of review under 35 USC §156(g)(1)(B)(i), the "Testing Period", began on February 6, 1995 and ended on December 16, 1999, which is 1,774 days or 4.86 years;

(ii) The period for review under 35 USC §156(g)(1)(B)(ii) the "Application Period", began on December 17, 1999 and ended on December 22, 2000, which is 372 days or 1.02 years;

(b) The regulatory review period upon which the period for extension is calculated is the entire regulatory review period as determined in sub-paragraph (13)(a) above (2146 days) less:

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (March 28, 1989), i.e. zero days, and

(ii) The number of days during which the Applicant did not act with due diligence, i.e. zero days, and

(iii) One half of the number of days remaining in the period in subparagraph (13)(a)(i) after subtracting the number of days in subparagraphs (13)(b)(i) and (13)(b)(ii), which is one half of (1774 - [0+0]) or 887 days;

which results in a period of 2146 - [0+0+887] = 1259 days or 3.45 years.

(c) The number of days as determined in sub-paragraph (13)(b), when added to the original term, would result in the date of September 7, 2009.

(d) Fourteen (14) years when added to the date of the NDA Approved Letter (December 22, 2000) would result in the date of December 22, 2014.

(e) The earlier date as determined by sub-paragraphs (13)(c) and (13)(d) is September 7, 2009.

(f) Since the original patent was issued after September 24, 1984, the extension otherwise obtainable is limited to not more than five years. Five years, when added to the original expiration of U.S. Patent No. Re. 34,878 (March 28, 2007) results in the date of March 28, 2011.

(g) The earlier date as determined in sub-paragraphs (13)(e) and (13)(f) is September 7, 2009.

14. Duty of Disclosure Acknowledgment under 37 CFR §1.740(a)(13)

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

15. Fee Charge

The prescribed fee for receiving and acting upon this application is to be charged to Applicant's Deposit Account 19-0134 as authorized in the attached transmittal letter, submitted in triplicate.

16. Correspondence Address Required by 37 CFR §1.740(a)(15)

All correspondence relating to this application for patent term extension should be addressed to:

Thomas Hoxie
Novartis Pharmaceuticals Corp.
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027

17. Certification under 37 CFR §1.740(a)(16)

The undersigned hereby certifies that the instant application, including its attachments and supporting papers, is being submitted as one original and one copy thereof in accordance with 37 CFR §1.740(a)(16).

18. Declaration under 37 CFR §1.740(a)(17)

The Declaration required by 37 CFR §1.740(a)(17) is attached hereto as "Appendix F".

Respectfully submitted,

Gregory D. Ferraro
Agent for Applicant
Reg. No. 36,134

Novartis Pharmaceuticals Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6923

Date: February 14, 2001

APPENDIX A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent Re. 34,878

Issued: March 14, 1995

To: Shigeshi Toyoshima, Yoshiko Seto, Hisashi Shinkai, Koji Toi and Izumi Kumashiro

For: HYPOGLYCEMIC AGENT

Box Patent Extension
Assistant Commissioner for Patents
Washington, D.C. 20231

POWER OF ATTORNEY

Sir:

Ajinomoto Co., Inc., a company organized and existing under the laws of Japan, and having its registered office at 1-15, Kyobashi, 1-Chome, Chuo-Ku, Tokyo, 104-8315, being the owner of the entire title and interest in and to U.S. Patent No. Re.34,878 which was granted on March 14, 1995 to Shigeshi Toyoshima, Yoshiko Seto, Hisashi Shinkai, Koji Toi and Izumi Kumashiro and entitled "HYPOGLYCEMIC AGENT", hereby appoints Novartis Corporation, a New York Corporation having offices at 608 5th Avenue, New York, N.Y. 10020, as its agent to act in its interest in this matter, and also appoints the attorneys and agents associated with Customer No. 001095, respectively and individually, each of them with full power of substitution and revocation, with regard to an application for extension of the term of U.S. Patent Re. 34,878 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Please direct all telephone calls to Gregory D. Ferraro at (908) 522-6923 and all correspondence to Thomas Hoxie at Novartis Pharmaceuticals Corporation, Patent and Trademark Dept., 564 Morris Avenue, Summits, N.J., 07901-1027.

AJINOMOTO CO., INC.

By: _____

Name: Tetsuo Kono

Title: General Manager
Intellectual Property Department

Date: February 5, 2001

APPENDIX B

US00RE34878E

United States Patent [19]

Toyoshima et al.

[11] E Patent Number: Re. 34,878

[45] Reissued Date of Patent: Mar. 14, 1995

[54] HYPOGLYCEMIC AGENT

[75] Inventors: Shigeshi Toyoshima; Yoshiko Seto, both of Funabashi; Hisashi Shinkai, Kawasaka; Koji Toi, Kanagawa; Izumi Kamashiro, Yokohama, all of Japan

[73] Assignee: Ajinomoto Co., Inc., Tokyo, Japan

[21] Appl. No.: 157,564

[22] Filed: Nov. 23, 1993

Related U.S. Patent Documents

Reissue of:

[64] Patent No.: 4,816,484
Issued: Mar. 28, 1989
Appl. No.: 146,719
Filed: Jan. 21, 1988

U.S. Applications:

[62] Division of Ser. No. 844,970, Mar. 27, 1989, abandoned.

[30] Foreign Application Priority Data

Mar. 27, 1985 [JP] Japan 60-62276

[51] Int. Cl.[6] A61K 31/215; C07C 101/72

[52] U.S. Cl. 514/563; 514/529; 514/530; 549/304; 549/467; 546/169; 546/323; 560/40; 560/41; 562/445; 562/450

[58] Field of Search 562/445; 560/40; 514/563, 613

[56] References Cited

U.S. PATENT DOCUMENTS

4,650,785 3/1987 Toyoshima et al. .
4,670,584 6/1987 Toyoshima et al. .

FOREIGN PATENT DOCUMENTS

93551 9/1983 European Pat. Off. .
2102412 2/1983 United Kingdom .

OTHER PUBLICATIONS

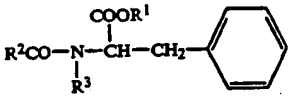
Toyoshima et al., "Preparation of D-Phenylalanine Derivatives and Their Use as Hypoglycemic Agents", CA 106 85057d (1987).

European Search Report/Application No. 86 30 2217/26-11-1987.

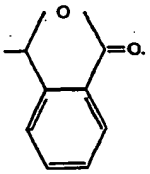
Primary Examiner—C. Warren Ivy
Assistant Examiner—A. A. Owens
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] ABSTRACT

A compound of D-phenylalanine derivative for hypoglycemic use, represented by the general formula



R^1 is selected from hydrogen, alkyl of 1 to 5 carbon atoms, aryl of 6 to 12 carbon atoms, aralkyl of 6 to 12 carbon atoms,



$-CH_2CO_2R^3$, $-CH(CH_3)-OCO-R^3$, and $-CH_2-OCO-C(CH_3)_3$; R^2 is selected from groups comprising aryl of 6 to 12 carbon atoms, a hetero six-membered ring, a hetero five-membered ring, cycloalkyl, or cycloalkenyl, any of which groups may have one or more substituents; and R^3 is selected from hydrogen and alkyl of 1 to 5 carbon atoms; the salts thereof, and precursors which can be converted thereto in the human or animal body.

Some of the compounds are novel per se.

16 Claims, No Drawings

HYPOGLYCEMIC AGENT

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

This application *is a Reissue of Ser. No. 07/146,719, filed Feb. 21, 1988, U.S. Pat. No. 4,816,182, which is a* divisional of Ser. No. 844,970, filed Mar. 27, 1986, now abandoned.

FIELD OF THE INVENTION

The present invention relates to hypoglycemic agents useful as antidiabetic drugs.

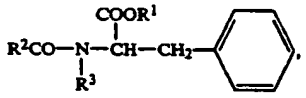
BACKGROUND TO THE INVENTION

Hitherto, as antidiabetic drugs for oral use, there have been widely employed sulfonyl urea which shows hypoglycemic action particularly through a promotion of the secretion of insulin, and a biguanide which shows a hypoglycemic action particularly through the metabolism of sugar. However, they are somewhat unsatisfactory as to their side effects (see Textbook of Endocrinology 4th ed., 1968, p. 719 (Saunders); Diabetes, 19, 785, 1970; Ann. Rev. Pharmacol., 15, 351, 1975).

No report has ben found that a D-phenylalanine derivative possesses hypoglycemic action.

SUMMARY OF THE INVENTION AND DESCRIPTION OF PREFERRED EMBODIMENTS

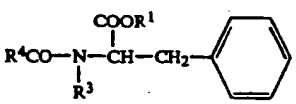
According to one aspect of the invention there is provided for pharmaceutical, particularly hypoglycemic, use, a D-phenylalanine derivative represented by the general formula:



(I)

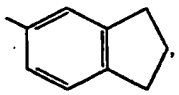
or a salt thereof, or a precursor which can be converted thereto in the human or animal body. Such compounds can lower the value of blood sugar and thus can be used as an antidiabetic drug for an oral use as well as by injection.

Among the foregoing phenylalanine derivatives, those in the D-form represented by the general formula:

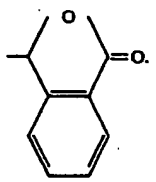


and the salts thereof are novel.

In the above general formulae: R^1 is hydrogen, alkyl of 1 to 5 carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, and sec-butyl, aryl of 6 to 12 carbon atoms such as phenyl, tolyl, naphthyl, and

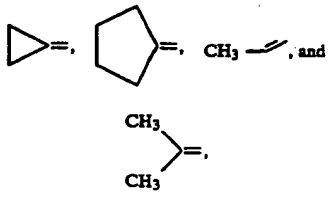


aralkyl of 6 to 12 atoms such as benzyl,



$-CH_2CO_2R^3$, $-CH(CH_3)-OCO-R^3$, or $-CH_2-OCO-C(CH_3)_3$, R^2 is a group comprising aryl of 6 to 12 carbon atoms such as phenyl, naphthyl, and indanyl, a hetero six-membered ring such as quinolynyl, pyridyl, a hetero five-membered ring such as 2-benzofuranyl, cycloalkyl such as cyclohexyl and cyclopentyl, bicycloalkyl such as bicycloheptye, and cycloalkenyl such as 1-cyclohexenyl, 2-cyclohexeneyl, 3-cyclohexenyl, 1-cyclopentenyl and 2-cyclopentenyl, any of which groups optionally having one or more substituents; R^3 is hydrogen or lower alkyl such as methyl, ethyl, isopropyl and pentyl; and R^4 stands for those R^2 groups which provide novel compounds hereof, notably phenyl which has one or more alkyl substituents of 2 to 5 carbon atoms, cyclohexyl which has one or more substituents cyclopentyl, bicycloalkyl, cycloalkenyl, indanyl or 2-benzofuranyl, any of which may have one or more substituents.

When an organic group in the above general formulae has a substituent, examples of such substituents include a halogen atom such as fluorine or chlorine, a hydroxyl group, a C_{1-5} alkyl group such as methyl, ethyl, trichloromethyl, trifluoromethyl, propyl, isopropyl, n-butyl, sec-butyl, and tert-butyl, a C_{1-5} alkenyl group such as ethenyl, propenyl, and butenyl, an alkylidene group such as



a C_{1-5} alkyloxy such as methoxy and ethoxy, a C_{1-5} alkyl group which has been substituted by such C_{1-5} alkyloxy group such as methoxymethyl and 1-ethoxyethyl, a C_{1-5} alkylene group which has been substituted by such C_{1-5} alkyloxy group in the same manner as above such as 1-methoxyethylene. In the case of a substituted bicycloalkyl group as stated above, it can include a bicycloheptyl or a derivative thereof such as bicyclo (2,2,1)heptyl.

In the case of the compound represented by the general formula (I) wherein R^1 stands for a hydrogen atom, it can be formed by conventional methods via the salts thereof with various cations such as an alkali metal, for example sodium and potassium, an alkali earth metal,

for example, calcium, an inorganic base, for example, ammonia, an organic base, for example, cyclohexylamine, N-methyl-D-glucosamine, or a basic amino acid (lysine, arginine and the like).

The D-phenylalanine derivative as shown by the formula (I) mentioned above, can be prepared by using conventional N-acylating reactions as in the Examples given below.

Most of the phenylalanine derivatives supplied by this invention are novel compounds which have not been described yet in the literature.

The D-phenylalanine derivatives used in the present invention are useful as a hypoglycemic agent for treating diabetic mammals including humans. The derivatives can be used for lowering blood sugar by formulating them into a preparation such as tablets, capsules, and elixirs for oral administration and into an aseptic liquid preparation or an aseptic suspension preparation for parenteral administration such as subcutaneous, intramuscular, intavenous injection, and suppositories. The D-phenylalamine derivatives in the present invention can be administered to a subject necessitating such treatment (animals and humans) in a dosage range of 0.1 to 1,000 mg per subject generally several times a day, that is, in a total daily dosage of 0.2 to 2,000 mg. The dosages varies according to the seriousness of disease, the body weight of subjects, and other factors acknowledged by those skilled in the art.

To produce the preparations using the D-phenylalanine derivatives as described above for the present invention, they may be converted to dosage forms such as tablets, granules, powders, capsules, injections and suppositories by conventional methods.

For the production of oral preparations, there may be added the to the D-phenylalanine derivative as the principal agent, adjuvants such as fillers, binders, disintegrators, lubricants, colors, and correctives, as necessary, and then formed by conventional methods into tablets, coated tablets, granules, powders, capsules and the like.

Examples of specific materials which can be incorporated into tablets, capsules, and so forth are as follows: fillers such as cornstarch, lactose, white sugar, glucose, sorbitol, and crystalline cellulose; binders such as polyvinyl alcohol, polyvinyl ether, ethyl cellulose, methyl cellulose, gum arabic, tragacanth gelatine, shellac, hydroxypropyl cellulose, hydroxypropyl starch, polyvinyl pyrrolidone; disintegrators such as starch, agar, gelatine powder, crystalline cellulose, calcium carbonate, sodium bicarbonate, calcium citrate, dextrin and pectin; lubricants such as magnesium stearate, talc, polyethylene glycol, silica, hardened plant oil; colors such as one which is allowed as an additive for the medicines; correctives such as cocoa powder, mentha herb, aromatic acid, mentha oil, borneol, cinnamon bark powder. These tables and granules may be coated with sugar, gelatine, or the like, as desired.

For the production of the injectable formulations, there may be added to the phenylalanine derivative as the principal agent, a pH adjusting agent, a buffer agent, a stabilizing agent, preservatives or the like, as necessary to produce a material for subcutaneous, intramuscular or intravenous injection by conventional methods.

EXAMPLES

The present invention will be further explained in the following examples.

EXAMPLE 1

N-(4-Ethylbenzoyl)-D-phenylalanine

D-Phenylalaine 2 g (12 mmole) was dissolved in 10% aqueous sodium hydroxide solution (10 ml), and acetone (10 ml) was added. An acetone (5 ml) solution of 4-ethyl benzoyl chloride (2.5 g, 15 mmole) and a 10% aqueous sodium hydroxide solution were added dropwise to the mixture obtained above while stirring and cooling with ice over 20 minutes, the reaction solution being maintained at pH 10. The reaction solution was returned to the room temperature, stirred for 3 hours, and made an acidic with a dilute hydrochloric acid solution to precipitate crystals. The crystals were filtered, washed with water and recrystallized from ethyl acetate to obtain N-(4-ethylbenzoyl)-D-phenylalanine (3.0 g, yield 83%).

m.p. 165.5°–166° C. Specific Rotation $[\alpha]_D^{23}+4.4°$ (C=1, methanol).

EXAMPLES 2 TO 11

For Examples 2 to 8, in the same manner as in Example 1, using the following starting materials, each compound of 50 mmole, the following product compounds were produced. The compounds in Examples 9 to 11 were already known, and therefore were produced in accordance with the following literature references:

Example 9: J. Amer. Chem. Soc., 73, 1644, 1951,
Example 10: Pol. J. Chem., 53, 2239, 1979, and
Example 11: J. Chromatogr., 264, 63, 1983.

Example No.	Starting Material	Product	Yield (%)	M.P. (°C.)	Specific Rotation
2	D-phenylalanine	N-(4-toldryl)-D-phenylalanine	83	152–155	$[\alpha]_D^{28}$ +46.2° (C = 0.5, methanol)
3	D-phenylalanine	N-(2-fluoro-benzoyl)-D-phenylalanine	74	91.5–93.5	$[\alpha]_D^{19}$ −8.8° (C = 1, methanol)
4	D-phenylalanine	N-(3-fluoro-benzoyl)-D-phenylalanine	81	112.5–116	$[\alpha]_D^{22}$ +48.6° (C = 1, methanol)
5	D-phenylalanine	N-(4-fluoro-benzoyl)-D-phenylalanine	80	142–145	$[\alpha]_D^{28}$ +40.4° (C = 0.5, methanol)
6	D-phenylalanine	N-(3-trifluoro-methylbenzoyl)-D-phenylalanine	77	118–119	$[\alpha]_D^{28}$ +40.4° (C + 1, methanol)
7	D-phenylalanine	N-(4-trifluoro-methylbenzoyl)-D-phenylalanine	70	136–137.5	$[\alpha]_D^{28}$ +36.3° (C = 1, methanol)
8	D-phenylalanine	N-4-anisoyl)-D-phenylalanine	65	85–90	$[\alpha]_D^{20}$ +60.2° (C = 0.5, methanol)
9	D-phenylalanine	N-benzoyl-D-	81		

-continued

Example No.	Starting Material	Product	Yield (%)	M.P. (°C.)	Specific Rotation
		phenylalanine			
10	D-phenylalanine	N-nicotinoyl-D-phenylalanine	62		
11	D-phenylalanine	N-(2-naphthoyl)-D-phenylalanine	83		

EXAMPLE 12

N-Cyclopentylcarbonyl-D-phenylalanine

Cyclopentane carboxylic acid (1.5 g, 13 mmole) was dissolved in chloroform (50 ml), and N-hydroxysuccinimide 1.7 g was added. N,N'-Dicyclohexylcarbodiimide (3.0 g) was gradually added to the mixture as obtained above while stirring and cooling with ice, and the mixture was stirred for 1 hour at the same temperature. The mixture was further stirred for 7 hours at room temperature. Glacial acetic acid (2 ml) was added to the mixture, and stirred for 1 hour. The insoluble matter was removed by filtration. The filtrate was washed with saturated aqueous sodium bicarbonate solution (30 ml), 1N aqueous hydrochloric acid solution (30 ml), and water (30 ml), and dried over magnesium sulfate. The magnesium sulfate was removed by filtration, and the solution thus obtained was concentrated under reduced pressure to dryness. The matter was recrystallized from ethyl acetate to afford cyclopentane carboxylic acid N-hydroxysuccinimide ester (2.5 g, yield 91%).

The ester derivative thus obtained above (2.5 g), was dissolved in chloroform (20 ml). This solution was added to a chloroform solution (40 ml) of D-phenylalanine methyl ester hydrochloride (3.0 g, 14 mmole) and triethylamine (1.4 g), and the mixture thus obtained was stirred for 18 hours at room temperature. The reaction solution was washed with 1N aqueous hydrochloric acid solution (40 ml), saturated aqueous sodium bicarbonate solution (40 ml) and water (40 ml), and dried over magnesium sulfate. The magnesium sulfate was removed by filtration and the filtrate was concentrated under reduced pressure to dryness. The matter was recrystallized from ethyl acetate-n-hexane to afford N-cyclopentylcarbonyl-D-phenylalanine methyl ester (3.0 g, yield 84%).

The methyl ester derivative (3.0 g) thus obtained above, was dissolved in methanol (10 ml), and 1N aqueous sodium hydroxide solution (20 ml) was added. The mixture was stirred for 30 minutes at room temperature and then made acidic with an addition of a dilute hydrochloric acid to precipitate crystals. The crystals were filtered, washed with water, and recrystallized from methanol-water to give the desired product (2.7 g, yield 80%).

m.p. 108°–110° C. Specific Rotation $[\alpha]_D^{22}-35.2°$ (C=0.5, methanol).

EXAMPLES 13 TO 18

For Examples 13 to 16, in the same manner as in Example 12, using as the starting material the following compounds, each of 15 mmole, the following products were obtained. The compounds of Examples 17 and 18 stated in the above table were known, and therefore were produced in accordance with the following literature references:

Example 17: BEXXA BELG. NO. 893553, 48, 1981, and

Example 18: Bull. Chem. Soc. Jpn., 57, 2171, 1984.

Example No.	Starting Material	Product	Yield (%)	M.P. (°C.)	Specific Rotation $[\alpha]_D^{22}$ (C = 0.5, methanol
13	2-benzofurane carboxylic acid	N-(2-benzofuranyl-carbonyl)-D-phenylalanine	59	114–116	+89.6°
14	5-indane carboxylic acid	N-(5-indanyl-carbonyl)-D-phenylalanine	64	160–161	+52.0°
15	3-cyclohexene carboxylic acid	N-(3-cyclohexenylcarbonyl-)D-phenylalanine	62	100–101	−12.6°
16	bicyclo-[2,2,1]heptan-2-ylcarboxylic acid	N-(bicyclo-[2,2,1]heptan-2-ylcarbonyl)-D-phenylalanine	50	179–181	+33.4°
17	cyclohexene carboxylic acid	N-cyclohexyl-carbonyl-D-phenylalanine	65		
18	benzoic acid	N-benzoyl-D-phenylalanine methyl ester	65		

EXAMPLE 19

N-(4-Isopropylcyclohexylcarbonyl)-D-phenylalanine

Platinum oxide (200 mg) as a catalyst was suspended in acetic acid (20 ml), and then (s)-(−)perillic acid (2 g, 12 mmole) was added. The mixture thus obtained was stirred for 8 hours at room temperature under a current of hydrogen gas. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to a dryness. The matter was recrystallized from methanol-water to obtain 4-isopropyl cyclohexane carboxylic acid (1.9 g, yield 93%).

After that, in the same manner as the reaction in Example 1, N-(4-isopropylcyclohexylcarbonyl)-D-phenylalanine was produced. It was crystallized from methanol-water to give the desired product (2.5 g, yield 61%).

m.p. 230°–232° C. Specific Rotation $[\alpha]_D^{22}$ −28.2° (C=0.5, methanol).

EXAMPLE 20

ICR-CDI mice (Male, five weeks old, Body weight: 20 g) which had been bred for one week, were abstained from food for 18 hours, and then used as test subjects.

The phenylalanine derivative of the present invention was suspended in 0.5% CMC-0.05M tris-hydrochloride buffer (pH 7.4). The sample solution thus obtained was administered orally in fixed amounts to the test subjects. A predetermined time later, the percentage decrease in blood glucose with the comparison to the control group was determined. The results are shown in the following table.

Example No.	Decrease in Blood Glucose (%) Amounts used (mg/kg)	60 Minutes
1	25	34
2	100	32
3	100	24
4	100	24
5	100	43
6	250	37
7	100	33
8	100	38
9	100	34
10	250	19
11	250	17
12	50	22
13	100	31
14	250	28
15	100	28
16	250	16
17	100	27
18	250	37
19	25	50

EXAMPLE 21

N-Cumoyl-D-Phenylalanine

Cumic acid (15.0 g, 91 mmole) was dissolved in chloroform (150 ml), and N-hydroxysuccinimide (11.4 g, 99 mmole) was added thereto. N,N'-Dicyclohexylcarbodiimide (20.4 g, 99 mmole) was added gradually to the mixture obtained above while cooling with ice and stirring, and then the mixture thus obtained was returned to room temperature. The mixture was further stirred for 15 hours at room temperature. Glacial acetic acid (5 ml) was added thereto, and the mixture thus obtained was stirred and the insoluble matter was removed by filtration. The filtrate was washed with saturated aqueous sodium bicarbonate (300 ml) and water (300 ml), and dried over magnesium sulfate. The magnesium sulfate was removed by filtration, and the filtrate thus obtained was concentrated under reduced pressure to dryness. The resultant substance was recrystallized from ethyl acetate to obtain cumic acid N-hydroxysuccinimide ester (18.8 g, yield 72 mmole).

The ester thus obtained above (18.8 g) was added to the chloroform solution (150 ml) of D-phenylalanine methyl ester hydrochloride (23.0 1 g, 110 mmole) and triethylamine (10.8 g, 110 mmole), and the mixture thus obtained was stirred for 15 hours at room temperature. The reaction solution was washed with 1N aqueous hydrochloric acid solution (300 ml), saturated aqueous sodium bicarbonate (300 ml) and water (300ml) and dried over magnesium sulfate. The magnesium sulfate thus used was removed by filtration, and the filtrate thus obtained was concentrated under reduced pressure to dryness.

The residue thus obtained was recrystallized from ethyl acetate-n-hexane to obtain N-cumoyl-D-phenylalanine methyl ester (20.5 g, yield 69%).

The methyl ester thus obtained above (20.5 g) was dissolved in methanol (100 ml), and then 1N aqueous sodium hydroxide (100 ml) was added thereto. The mixture thus obtained was stirred for 10 minutes at room temperature, and was made acidic with an addition of diluted aqueous hydrochloric acid solution to precipitate crystals. The crystals were filtered, washed with water and recrystallized from methanol-water to give the desired product (18.1 g, yield 64%).

m.p. 177°–178° C. Specific Rotation $[\alpha]_D^{20}$ +25.5° (C=1, methanol).

EXAMPLES 22 to 30

In the same manner as in Example 21, using as the starting material the following compounds, each at 50 mmole, the following product compounds were produced.

Example No.	Starting Material	Product	Yield (%)	M.P. (°C.)	Specific Rotation $[\alpha]_D^{20}$ (C = 1, methanol)
22	(s)-perillic acid	N-[(s)-perilloyl]-D-phenylalinine	44	109–110	−37.2°
23	trans-4-n-propylcyclohexane carboxylic acid	N-(trans-4-n-propylcyclohexylcarbonyl)-D-phenylalanine	48	104–105	−8.8°
24	trans-4-n-butylcyclohexane carboxylic acid	N-(trans-4-n-butylcyclohexylcarbonyl)-D-phenylalanine	50	144–145	−7.5°
25	4-tert-butylbenzoic acid	N-(4-t-butylbenzoyl)-D-phenylalanine	55	177–178	+51.5°
26	cuminic acid	N-cumoyl-L-phenylalanine	63	121–123	$[\alpha]_D^{23}$ −29.3° (C = 1, methanol)
27	cyclopentane carboxylic acid	N-cyclopentylcarbonyl-L-phenylalanine	40	115–117	$[\alpha]_D^{23}$ −30.1° (C = 1, methanol)
28	trans-4-methyl-cyclo-	N-(trans-4-methylcyclohexyl-	43	124–125	$[\alpha]_D^{23}$ −11.5° (C = 1, methanol)

-continued

Example No.	Starting Material	Product	Yield (%)	M.P. (°C.)	Specific Rotation
	hexane carboxylic acid	carbonyl)-D-phenylalanine			
29	trans-4-ethylcyclohexane carboxylic acid	N-(trans-4-ethylcyclohexyl-carbonyl)-D-phenylalanine	53	96–97	$[\alpha]_D^{23}$ −11.1° (C = 1, methanol)
30	trans-4-t-butyl-cyclohexane carboxylic acid	N-(trans-4-t-butylcyclohexyl-carbonyl)-D-phenylalanine	49	160–161	$[\alpha]_D^{23}$ −9.0° (C = 1, methanol)

EXAMPLE 31

N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine

Platinum oxide (500 mg) as a catalyst was suspended in acetic acid (50 ml) and cumic acid (10 g, 61 mmole) was added thereto. The mixture thus obtained was stirred vigorously for 2 hours at room temperature under a pressure of hydrogen 5 kg/cm². The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to a solid state. The resultant substance was distilled under reduced pressure of 1 mmHg (1.3×10^{-3} kg/cm²), at 113°–116° C. to obtain 4-isopropylcyclohexane carboxylic acid yielding 10 g (96%) in a ratio of 3 parts of cis-form per 1 part of trans-form by weight.

To methanol (70 ml) at less than −20° C., thionyl chloride (17 ml) was added dropwise, and the carboxylic acid (10 g) as obtained above was added. The mixture thus obtained was stirred for 15 hours at room temperature, and then concentrated under reduced pressure to a solid substance. The substance thus obtained was distilled under reduced pressure of 0.7 mmHg (9.2×10^{-4} kg/cm²) at 66° C. to obtain 4-isopropylcyclohexane carboxylic acid methyl ester (9.5 g, yield 88%).

To the methyl ester (b 9.5 g) thus obtained, sodium hydride (120 mg) was added, and the mixture was heated at 150° C. for 2 hours under a current of nitrogen gas. The reaction solution was cooled and then subjected to a reduced pressure distillation of 0.7 mmHG (9.2×10^{-4} kg/cm²) at 66° C. to obtain 4-isopropylcyclohexane carboxylic acid methyl ester in a ratio of 6 parts trans-form per 1 part cis-form.

The methyl ester (9.0 g) thus obtained was dissolved in methanol (50 ml), and 1N aqueous sodium hydroxide solution (50 ml) was added thereto. The mixture thus obtained was stirred for 10 minutes at room temperature and made acidic with an addition of a dilute aqueous hydrochloric acid solution to precipitate crystals. The crystals were filtered, washed with water, and crystallized from methanol-water to give trans-4-isopropylcyclohexane carboxylic acid (6.8 g, yield 78%).

After that, in the same manner as in Example 21, using as a starting material the carboxylic acid derivative (6.8 g, 40 mmole), N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine was produced, and recrystallized from methanol-water to give the desired product (8.2 g, yield 65%).

m.p. 129°–130° C. Specific Rotation $[\alpha]_D^{20}$ −9.4° (C=1, methanol).

EXAMPLES 32 TO 35

In the same manner as in Example 26, using as the starting material the following compounds, each of 40 mmole, the following product compounds were produced.

Example No.	Starting Material	Product	Yield (%)	M.P. (°C.)	Specific Rotation $[\alpha]_D^{20}$ (C = 1, methanol)
32	trans-4-isopropyl-cyclohexane carboxylic acid	4-(trans-4-isopropylcyclo-hexylcarbonyl)-D-phenylalanine methyl ester	52	137–138	+8.8°
33	trans-4-isopropyl-cyolohexane carboxylic acid	N-(trans-4-isopropylcyclo-hexylcarbonyl)-L-phenylalanine	56	130–131	+9.5°
34	trans-4-isopropyl-cyclohexane carboxylic acid	N-(trans-4-isopropylcyclo-hexylcarbonyl)-2-phenylethylamine	66	134—135	—
35	trans-4-isopropyl-cyclohexane carboxylic acid	N-(trans-4-isopropylcyclo-hexylcarbonyl)-D-phenylalanine benzylester	58	129—130.5	+8.4°

EXAMPLE 26

N-(Cis-4-isopropylcyclohexylcarbonyl)-D-phenylalanine

4-Isopropylcyclohexane carboxylic acid methyl ester (9.5 g) (Cis-form:trans-form=3:1) was obtained in the same manner as in Example 26. Cis-4-isopropylcyclohexane carboxylic acid methyl ester (7 g) was ob-

tained from the product thus obtained by a high performance liquid chromatography of YMC A-043 column using as the solvent a mixture of n-hexane and 1,2-dichloro ethane in a ratio of 75:25.

After that, in the same manner as in Example 21, using as a starting material the cis-form thus obtained (6.5 g, 38 mmole), N-(Cis-4-isopropylcyclohexylcarbonyl)-D-phenylalanine was produced, and recrystallized from methanol-water to give the desired product (8 g, yield 66%).

m.p. 111°–112° C. Specific Rotation $[\alpha]_D^{20}$ −13.2° (C=1, methanol).

EXAMPLE 37

ICR-CDI mice (Male, five weeks old, Body weight: 20 g) were abstained from food for 18 hours, and then used as test subjects.

The phenylalanine derivative of the present invention was suspended in 0.5% CMC-0.14M sodium chloride buffer solution (pH 7.4). The solution thus obtained was administered orally in fixed volume amounts to the test subjects. After a predetermined time, the percentage decrease of the blood glucose against the control group was determined. The results are shown in the following Table.

Example No.	Amounts used in sample mg/kg body weight	Decrease in blood glucose after 60 minutes (%)
21	25	26
22	100	43
23	100	35
24	100	30
25	100	32
26	100	0
27	100	0
28	6.25	24
29	6.25	31
30	6.25	30
31	1.5	30
32	6.25	37
33	100	23
34	100	14
35	25	24
36	100	27

It is clear from the foregoing that the D-phenylalanine derivatives as described above can be used as an antidiabetic drug for oral administration as well as the more usual parenteral administration.

We claim:

1. A D-phenylalanine derivative of the formula

$$R^4—CO—NR^3—CH(COOR^1)—CH_2—C_6H_5$$

or a salt thereof or a precursor which can be converted into said D-phenylalanine derivative in vivo, wherein:

R^1 is hydrogen or C_{1-5} alkyl,

Ris hydrogen or C_{1-5} alkyl; and

R^4 is cyclohexane substituted at the 4- or 5-position by methyl, ethyl, ispropyl, tert-butyl, ethene, or isopropene or cyclohexene substituted at the 4- or 5-position by methyl, ethyl, isopropyl, tert-butyl, ethene, or isopropene.

2. The D-phenylalanine derivative of claim 1, wherein R^4 is said substituted cyclohexane.

3. The D-phenylalanine derivative of claim 1, wherein R^4 is said substituted cyclohexane.

4. The D-phenylalanine derivative of claim 1, wherein the said derivative is N-(4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

5. The D-phenylalanine derivative of claim 1, wherein the said derivative is N-(4-isopropylcyclohexylcarbonyl)-D-phenylalanine: N-[(S)-perilloyl]-D-phenylalanine; N-(4-methylcyclohexylcarbonyl)-D-phenylalanine; N-(4-ethylcyclohexylcarbonyl)-D-phenylalanine; or N-(4-t-butylcyclohexylcarbonyl)-D-phenylalanine.

6. The D-phenylalanine derivative of claim 1, wherein the said derivative is N-[(s)-perilloyl]-D-phenylalanine; N-(trans-4-methylcyclohexylcarbonyl)-D-phenylalanine; N-(trans-4-ethylcyclohexylcarbonyl)-D-phenylalanine; N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine; or N-(trans-4-t-butylcyclohexylcarbonyl)-D-phenylalanine.

7. The D-phenylalanine derivative of claim 1, wherein R^1 is hydrogen and R^3 is hydrogen.

8. The D-phenylalanine derivative of claim 1, wherein R^4 is perilloyl.

9. The D-phenylalanine derivative of claim 1, wherein said substituted cyclohexane is substituted at the 4-position.

10. The D-phenylalanine derivative of claim 1, wherein said substituted cyclohexane is substituted at the 5-position.

11. The D-phenylalanine derivative of claim 1, wherein said substituted cyclohexene is substituted at the 4-position.

12. The D-phenylalanine derivative of claim 1, wherein said substituted cyclohexene is substituted at the 5-position.

13. The D-phenylalanine derivative of claim 1, wherein said substituted cyclohexane or said substituted cyclohexene is substituted with methyl, ethyl, isopropyl or tert-butyl.

14. The D-phenylalanine derivative of claim 1, wherein said substituted cyclohexane or said substituted cyclohexene is substituted by ethene, or isopropene.

15. A pharmaceutical composition, comprising a D-phenylalanine derivative of claim 1 and a pharmaceutical excipient.

16. The compound N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

APPENDIX C

PATENT NO. : RE34878
DATED : March 14, 1995
INVENTOR(S) : Shigeshi TOYOSHIMA, et al.

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

On the title page, Item [62], the Related U.S. Application Data should read:

--Division of Ser. No. 844,970, Mar. 27, 1986, abandoned.--

Signed and Sealed this

Thirtieth Day of May, 1995

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

APPENDIX D

UNITED STATES DEPARTMENT OF COMMERCE
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000146

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MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.
If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(h).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	RE 34,878	185	2910	----	08/157,564	03/14/95	11/23/93	12	NO	PAID

ITM NBR	ATTY DKT NUMBER
1	10635OREISSU

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO: COMMISIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, D.C. 20231

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If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM SR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	RE 34,678 (4,816,484)	184	1990	----	08/157,504 (07/146,719)	08/14/95 (03/28/89)	11/23/93 (01/21/88)	08	NO	PAID PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and an explanation below....

IND Index

Starlix IND 47,235

Date	Description	Protocol #	AR #	LOCATION	AMEND	REC. ID/ORDER
		(* Indicates more than one occurrence)				
05/11/98	FAXED to the FDA a copy of the ADA's Nutritional Guide per telephone request of 5/8/98.					41653 / 1
05/27/98	Submitted a change in site address for Dr. Wild for Protocol B302-E-00.	B302-E-00			102	42217 / 1
05/27/98	Submitted the following new investigators to Protocol B351-E-00: Drs. Dean, Franklin.	B351-E-00			102	42217 / 2
05/27/98	Also submitted the following new investigators to Protocol B356-E-00: Drs. Clinkingbeard, Crandall, Dwarakanathan, Ervin, Farrell, Freedman, Garza, Haag, Harb, Hutchins, Kern, Kluge, Lodewick, Mangione, Meneghini, Mikolich, Morton, Ott, Parker, Perloff, Plasko, Rendell, Rosansky, Sack, Schumacher, Schwartz, Shane, Smith, Steinbrenner, Sullivan, Suwannasri, Truitt, Williams. Also added three new subinvestigators for Dr. Knoph.	B356-E-00			102	42217 / 4
05/28/98	New Protocol DJNW-366, "A Randomized, Open-Label, Five- Period Crossover Study to Compare the Pharmacodynamic and Pharmacokinetic Effects of SDZ DJN 608, Repaglinide and Placebo in Healthy Subjects." Also submitted the following new principle investigator: Dr. Lasseter.	366			103	42218 / 1
06/02/98	Submitted Amendment No. 4 to Protocol DJNW-353. Also submitted the following new investigator: Dr. Zeig.	353			104	42219 / 1
06/18/98	New Protocol DJNW-361, "A Four-Phase, Eight-Period, Open-Label, Randomized, Crossover Study to Compare the Effects of SDZ DJN with Glyburide on the Beta-Cell Sensitivity of Healthy Subjects at Different Clamped Plasma Concentrations of Glucose." Also submitted the following new principal investigator: Dr. Shah.	361			105	42220 / 1

IND Index

Starlix IND 47,235

Date	Description	Protocol #	AR #	LOCATION	AMEND	REC. ID/ORDER
		(* Indicates more than one occurrence)				
06/19/98	FDA FAX: Review of the clinical section of IND submission dated June 2, 1998, protocol 353 Amendment #4.	353				42534 / 1
06/19/98	TELECON with Ms. Weber to discuss planning for a pre-NDA meeting with the Division.					42534 / 1
07/06/98	Submitted the following new investigators to Protocol B302-E-00: Drs. Strojek, Serusclat, Czyzyk, Drzewoski, Kucharz, Penet. Also submitted new addresses for Drs. Rubino, Lodewick, Toth. Along with a new subinvestigator for Dr. Weiss.	B302-E-00			106	42534 / 1
07/06/98	Also submitted the following new investigators to Protocol B351-E-00: Drs. Noss, Arcuri, McCarty, Touger. Also submitted a new subinvestigator for Dr. Caffrey and a change of adress for Dr. Hippert.	B351-E-00			106	42534 / 7
07/06/98	Also submitted the following new investigators to Protocol B354-E-00: Drs. Ittner, Chouravi, Krakow, Cambau, Penet, Pommet-Nicot, Serusclat, Bajard, Bully, Hugues, Brochud.	B354-E-00			106	42534 / 11
07/06/98	Also submitted new subinvestigators to Protocol B355-E-00 for Drs. Kirby, Herbst, Kaplan.	B355-E-00			106	42534 / 22
07/06/98	Also submitted the following new investigators to Protocol B356-E-00: Drs. Geller, Chaykin, Robbins, Hall, Thwainey. Also submitted new subinvestigators to Dr. LaCava and Weinstein.	B356-E-00			106	42534 / 23

Date	Description	Protocol #	AR #	LOCATION	AMEND	REC. ID/ORDER
	(* Indicates more than one occurrence)					
07/10/98	Submitted amendment consisting of Chemistry, Manufacturing and Controls information to support the use of a placebo tablet to match the Metformin tablet comparative agent formulation in Protocol B351. Also included the following document: Placebo Metformin Tablet-FCN/KN 3746328.00.002.B, dated July 9, 1998.				107	42628 / 1
07/20/98	New Protocol DJN B304-E-00, "A Multicenter, Double-Blind, Randomized, Parallel-Group, Fixed Dose Study to Prospectively Evaluate the Efficacy, Safety and Tolerability of Two Doses of SDZ DJN 608 Monotherapy Compared to Glibenclamide Monotherapy in Subjects with Type 2 Diabetes Previously Treated with Diet and Sulfonylureas."	B304-E-00			108	42839 / 1
07/20/98	Also submitted Amendment No. 1 to Protocol DJN B304-E-00 and the following new investigator: Dr. Rosenblatt.	B304-E-00			108	42839 / 2
07/20/98	Also submitted responses per FDA request on girth measurements and method for measurement of lipid fractions.	B356			108	42839 / 3
07/30/98	Annual Report covering the period of February 7, 1997 to February 6, 1998. Includes: Individual Study Information, Clinical Studies Not Conducted Under the IND, Summary of Safety Information, List of Deaths and Dropouts, Dose Response or Bioavailability Information - Clinical, Preclinical Studies, General Investigational Plan for the Coming Year, Investigator's Brochure.				109	42979 / 1
07/30/98	TELECON with Dr. Koller to discuss Novartis' response to Dr. Koller's question (fax of 5/11/98) about the methodology for taking hip and waist girth measurements in protocol B356 (dated 7/20/98); also on the glibenclimide dose in protocol B304 (dated 7/20/98); and Dr. Koller's concerns regarding investigator qualifications.					43127 / 1

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Date	Description	Protocol #	AR #	LOCATION	AMEND	REC. ID/ORDER
	(* Indicates more than one occurrence)					
08/10/98	FAX to Dr. Koller regarding implementation of the latest changes for the package insert into protocol B356. Also included a proposal not to routinely discontinue patients from Novartis' trial solely due to inadequate response.					43559 / 1
08/12/98	New Protocol DJNW-363, "A Randomized, Double-Blind, Placebo-Controlled, Three-Period Crossover Study to Compare the Pharmacodynamic Effects of SDZ DJN 608, Glyburide and Placebo in Type 2 Diabetic Subjects in the Event of a Missed Lunch-Time Meal and a Dose of SDZ DJN 608."	363			110	43560 / 1
08/12/98	Also submitted the following new investigators to Protocol B302-E-00: Drs. Bajard, Cambau.	B302-E-00			110	43560 / 2
08/12/98	Also submitted the following new investigators to Protocol B304-E-00: Drs. Elinoff, Guerin, Littljohn, Lodewick, Rosenblatt.	B304-E-00			110	43560 / 4
08/12/98	Also submitted the following new investigators to Protocol B354-E-00: Drs. Bernard, Schmitt, Gerber, Grosskopf, Bouvier, Brunel-Roche, Roux.	B354-E-00			110	43560 / 9
08/12/98	Also submitted new subinvestigator and changes to Protocol B355-E-00 for Dr. Herbst.	B355-E-00			110	43560 / 16
08/12/98	Also submitted the following new subinvestigators to Protocol B356-E-00: Drs. Weissman, DeHaven, Phillips, Lillienfeld.	B356-E-00			110	43560 / 17

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Date	Description	Protocol #	AR #	LOCATION	AMEND	REC. ID/ORDER
		(* Indicates more than one occurrence)				
10/6/98	FDA FAX: Comments and requests for the clinical section of the annual report dated July 30, 1998.					45004 / 1
08/17/98	In follow up to a teleconference with Dr. Koller to discuss revisions to be made to Starlix Protocol B356 labeling changes, provided information regarding the amendment to be made in order to address the Division's concerns.	B356				43561 / 1
08/25/98	New Protocol DJNW-367, "A double-blinded, three period, placebo-controlled, randomized, crossover study to evaluate the effect of SDZ DJN 608 and glyburide on basal and postprandial hepatic glucose production and lipolysis in patients with NIDDM." Also submitted the following new investigator: Dr. Kelley.	367			111	43562 / 1
08/28/98	New Protocol DJNW-363, "A randomized, double-blind, placebo-controlled, three-period crossover study to compare the pharmacodynamic effects of SDZ DJN 608, glyburide and placebo in type 2 diabetic subjects in the event of a missed lunch-time meal and missed dose of SDZ DJN 608." Also submitted the following new investigator: Dr. Zeig.	363			112	43563 / 1
08/31/98	Submitted Amendment No. 2 to Protocol DJN 356B-E-00.	356B-E-00			113	43564 / 1
09/16/98	Submitted the following new investigators to Protocol B302-E-00: Drs. Scherbaum, Schell.	B302-E-00			114	43921 / 1
09/16/98	Also submitted Amendment No. 2 to Protocol B304-E-00. Also submitted the following new investigators: Drs. Bortz, Dobs, Giffin, Meneghini, Kirby, McGill, Ramirez, Rosenstock, Schwartz, Wigand.	B304-E-00			114	43921 / 3

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Date	Description	Protocol #	AR #	LOCATION	AMEND	REC. ID/ORDER
	(* Indicates more than one occurrence)					
09/16/98	Also submitted the following new investigator to Protocol B354-E-00: Dr. Schell.	B354-E-00			114	43921 / 13
09/16/98	Also submitted new subinvestigators for Drs. Kirby and Bell to Protocol B355-E-00.	B355-E-00			114	43921 / 14
09/16/98	Also submitted the following new investigators to Protocol B356-E-00: Drs. Dobs, Galloway, Gorson.	B356-E-00			114	43921 / 15
09/25/98	TELECON with FDA Pharmacologist Dr. Rhee regarding NVP DPP 728 IND. Novartis is in the process of investigating the neuronal degeneration in Starlix mouse carc. study, as was agreed by FDA.					44438 / 1
10/06/98	New Protocol W365-E-00, "Randomized placebo-controlled, five- period study to determine the effects of SDZ DJN 608 on the first-phase insulin response to intravenous glucose, in comparison to glyburide, in subjects with type 2 diabetes mellitus." Also submitted the following new investigator: Dr. Kahn.	W365-E-00			115	43937 / 1
10/06/98	Also submitted the following new investigators to Protocol B356-E-00: Drs. Raskin, DeGarmo, Brigham, Fiorillo, Gillie, Lefton, Cohen, Gutierrez, Taylon, Barrera.	B356-E-00			115	43937 / 2
10/26/98	Submitted CMC information amendment consists of updated technical documentation including analytical methodology, formulation information, and Section F of the IND annual report.				116	44439 / 1

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Date	Description	Protocol #	AR #	LOCATION	AMEND	REC. ID/ORDER
	(* Indicates more than one occurrence)					
10/26/98	Also submitted composition, manufacturing formula and method of preparation - KN 3741865.00.012.1 and KN 3741865.00.0011H for matching placebo for the 60 and 120 mg Starlix tablets.				116	44439 / 2
10/27/98	Submitted a copy of the meeting minutes for the 10/27/98 Starlix NDA Planning Meeting.					45010 / 1
10/27/98	Submitted a copy of the meeting minutes held on 10/27/98 regarding HPB and Clinical Pharmacology sections of the NDA for the pre-NDA meeting with FDA for 1/99 and familiarize line unit representative with the NDA guidelines, Novartis procedures and DRS's NDA tracking sheet.					45483 / 1
10/29/98	New Protocol CDJN608 0118, "A two-period, open-label, randomized, crossover study to evaluate the bioequivalence of two 120 mg SDZ DJN 608 tablet formulations.	0118			117	44441 / 1
10/29/98	Also submitted Amendment No. 1 to Protocol CDJN608 0118.	0118			117	44441 / 2
10/29/98	Also submitted the following new investigator to Protocol CDJN608 0118: Dr. Hunt.	0118			117	44441 / 3
10/29/98	Also submitted New Protocol CDJN608 0119, " A three-period, open-label, randomized, crossover study to evaluate the bioequivalence of three 180 mg SDZ DJN 608 tablet formulations."	0119			117	44441 / 4
10/29/98	Also submitted Amendment No. 1 and the following new investigator to Protocol CDJN608 0119: Dr. Hunt.	0119			117	44441 / 5

Date	Description	Protocol #	AR #	LOCATION	AMEND	REC. ID/ORDER
		(* Indicates more than one occurrence)				
10/29/98	Also submitted New Protocol CDJN608 0123, "A two-period, open-label, randomized, crossover study to evaluate the bioequivalence of two 60 mg SDZ DJN 608 tablet formulations."	0123			117	44441 / 6
10/29/98	Also submitted Amendment No. 1 and the following new investigator to Protocol CDJN608 0123: Dr. Talluir.	0123			117	44441 / 7
10/29/98	Also submitted chemistry documentation in support of the 60, 120 and 180 mg tablet formulations (KN 3741287.00.016.J, KN 3742038.00.009.C and KN 3744844.00.008.C) for use in protocols 0118, 0119, and 0123. Also included the information on the composition, sites of manufacture, packaging and controls, manufacturing formula and method of manufacture, specifications and controls procedures for the drug product and components, description of the container and stability.	118,119,123			117	44441 / 8
11/04/98	Submitted responses to a fax received from the FDA on 10/6/98 that contained comments and requests for information regarding Novartis' annual report dated 7/20/98, serial number 109.				118	45019 / 1
11/16/98	Submitted the following new investigator to Protocol B302: Dr. Karnafel (replaced Dr. Czyz as Principal Investigator).	302			119	45020 / 1
11/16/98	Also submitted the following new investigator to Protocol B354: Dr. Lingard.	354			119	45020 / 2

Date	Description	Protocol #	AR #	LOCATION	AMEND	REC. ID/ORDER
		(* Indicates more than one occurrence)				
11/16/98	Also submitted the following new investigators to Protocol B356: Drs. Einhorn, Heatley, Peterson, Aronoff.	356			119	45020 / 3
11/16/98	Also submitted changes to the subinvestigators to protocol DJNW-363 for Dr. Zeig.				119	45020 / 7
11/16/98	Submitted the following new investigator to Protocol B302: Drs. Karnafel (replacing Dr. Czyz).	302			119	45484 / 1
11/16/98	Also submitted the following new investigator to Protocol B354: Dr. Lingard.	354			119	45484 / 2
11/16/98	Also submitted the following new investigators to Protocol B356: Drs. Einhorn, Heatley, Peterson, Aronoff.	356			119	45484 / 3
11/16/98	Also submittted changes to Protocol DJNW-363 for Dr. Zeig	363			119	45484 / 7
12/07/98	Submitted an amendment to the stability protocol issued Febraury 10, 1998 under serial #096.				120	45485 / 1
12/14/98	Submitted new protocol: Protocol DJNW-364, A two phase, five period, randomized, placebo-controlled, dose-escalating study to determine the dose dependence of the pharmacodynamic response to single oral doses of SDZ DJN 608 at moderately elevated blood glucose levels in subjects with type 2 diabetes mellitus.	DJNW-364			121	45602 / 1
12/14/98	Also submitted the following new investigators to Protocol B354: Drs. Gheron, Lemaire.	B354			121	45602 / 2

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Date	Description	Protocol #	AR #	LOCATION	AMEND	REC. ID/ORDER
	(* Indicates more than one occurrence)					
12/14/98	Also submitted the following new investigator to Protocol B356-E-00: Dr. Clevinger.	B356-E-00			121	45602 / 3
12/14/98	Also submitted Amendment 3 to Protocol B356-E-00.	B356-E-00			121	45602 / 4
12/14/98	Also submitted various new subinvestigators to Protocols B302-E-00 and B304-E-00 in addition to providing a new lab site to Protocol B355-E-00.	X			121	45602 / 5
12/23/98	Additional briefing/background information regarding netaglinide and the remaining issues Novartis would like to discuss with the FDA on January 19, 1999.			BK 23	122	45546 / 1
01/05/99	Correspondence requesting review by the Labeling and Nomenclature Committee of the proprietary name Starlix which Novartis has selected for nateglinide oral tablets.				123	46034 / 1
01/14/99	Faxed correspondence which contains the list of the Novartis representatives who will be attending the pre-NDA meeting scheduled for January 19, 1999.					46035 / 1
02/12/99	New Protocol CDJN6080116, "A multicenter, double-blind, randomized, parallel-group study to evaluate the efficacy, safety and tolerability of three fixed dose levels of nateglinide and placebo in type 2 diabetes mellitus patients with minimally elevated fasting plasma glocuse levels". Also provided for Dr. Hershon.	0116			124	46037 / 1
02/18/99	Novaartis' minutes of the January 19, 1999 pre-NDA meeting with the FDA.				125	46036 / 1

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Date	Description	Protocol #	AR #	LOCATION	AMEND	REC. ID/ORDER
		(* Indicates more than one occurrence)				
03/10/99	Amendment 2 to Protocol B302 which provides for an update to the section covering the statistical analysis.	302			126	47181 / 1
03/10/99	Also: Amendment 3 to Protocol B304 which provides for an update to the section covering the statistical analysis.	304			126	47181 / 2
03/10/99	Also: Amendment 3 to Protocol B351 which provides for an update to the sections covering the statistical analyses.	351			126	47181 / 3
03/10/99	Also: Amendment 1 to Protocol B355 which provides for an update to the sections covering the statistical analyses.	355			126	47181 / 4
03/10/99	Also: Amendments 4 and 5 to Protocol B356.	356			126	47181 / 5
03/10/99	Also submitted the following new investigator to Protocol B356: Dr. Enejosa.	356			126	47181 / 6
03/10/99	Also: Amendment 1 to Protocol DJNW-365.	DJNW-365			126	47181 / 7
03/10/99	Also submitted the following new investigators to Protocol CDJN608-0116: Drs. Arcuri, Azorr, Barrera, Booras, Garza, Drucker, Rictor, Kilo, LeLevier, Littlejohn, Marbury, Morin, Oandasan, Weinstein, Williams.	CDJN608-0116			126	47181 / 8
03/29/99	TELECON TO FDA requesting that FDA inform Novartis if a formal decision for a label change is made for troglitazone which would impact on the study design for Protocol B356.	B356				47677 / 1

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Date	Description	Protocol #	AR #	LOCATION	AMEND	REC. ID/ORDER
		(* Indicates more than one occurrence)				
04/05/99	New Protocool DJNW364, "A two phase, five period, randomized, placebo controlled, dose-escalating study to determine the dose dependence of the pharmacodynamic response to single oral doses of SDZ DJN 608 at moderately elevated blood glucose levels in subjects with type 2 diabetes mellitus". Also included Amendment 1 and documentation for Dr. Gerich, new investigator.	364			127	47171 / 1
04/15/99	New protocol, Study CDJN6080124, "A two treatment sequence, four-period, open label, randomized, crossover study to evaluate the bioequivalence of two 60 mg SDZ DJN 608 tablet formulations". Also provided for Tariq Sultan, MD.	0124			128	47688 / 1
04/15/99	Also included new protocol, Study CDJN6080125, "A two treatment sequence, four-period, open-label, randomized, crossover study to evaluate the bioequivalence of two 180 mg SDZ DJN 608 tablet formulations. Also provided for Leonard Lachman, MD.	0125			128	47688 / 2
04/27/99	Faxed correspondence requesting a teleconference with the Medical Reviewer to discuss specific questions as described regarding the ongoing Protocol B356.	B356				48205 / 1
04/28/99	Protocol CDJ N608 0116, Substudy 1, "An evaluation of prandial metabolic and coagulation parameters in type 2 diabetes mellitus patients with mildly elevated fasting plasma glucose levels treated with three fixed dose levels of nateglinide and placebo".	116/SUBSTDY1			129	47696 / 1

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Date	Description	Protocol #	AR #	LOCATION	AMEND	REC. ID/ORDER
		(* Indicates more than one occurrence)				
04/28/99	Also provided for the following new investigators for Protocol 0116: Jonathan D. Bortz, MD, Harold K. Cathcart, DO, Sidney Clevinger, MD, Anthony B. Fiorillo, MD, Andrew Ahmann, MD, Timothy M. Howard, MD, Dennis C. McCluskey, MD, Jeffrey D. Wayne, MD.	0116			129	47696 / 2
04/28/99	Also provided for David Lackner, MD, principal investigator for Study B351-E-00.	B351			129	47696 / 3
04/28/99	Also included Amendment 3 to Study B354	B354			129	47696 / 4
04/28/99	Chemistry, Manufacturing and Controls information in support of Protocol W373. Included documentation for Repaglinide 2 mg capsules, 3755501.00.001.A, drug product comparator and matching placebo capsules, 3755030.00.004.A, dated 1-Apr-1999.	W373			130	48209 / 1
05/07/99	Submitted the following CMC incormation in support of Protocol 103: Description, composition and manufacturing formula Metformin 500 mg tablet (drug product comparator) KN 3746310.00.004; Placebo metformin 500 mg tablet, KN 3746328.00.004; Starlix 120 mg tablet KN 3742038.00.010.C; Placebo matching the Starlix 120 mg tablet, KN 3741865.00.013.H, 30-Apr-1999.	103			131	47892 / 1
05/10/99	New Protocol, Study No. CDJN6080103, A multicenter, double-blind, randomized parallel-group fixed dose study to prospectively evaluate the efficacy, safety and tolerability of nateglinide monotherapy, compared to metformin monotherapy in patients with Type 2 diabetes mellitus inadequately controlled with diet.	103			132	47890 / 1

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Date	Description	Protocol #	AR #	LOCATION	AMEND	REC. ID/ORDER
		(* Indicates more than one occurrence)				
05/10/99	Also included Amendment 1 to Protocol 103.	103			132	47890 / 2
05/10/99	Also included the following investigators: Joan Brigham, MD, Lydia G. Corn, MD, Maria J. Gutierrez, MD, James T. Hawa, D.O., Abe Marcadis, MD, Michael McCartney, MD, Sundara Rajan, MD, Peter M. Ripley, MD, David Gerald Robertson, MD, Julio Rosenstock, MD, Michael D. Stadiem, MD.	103			132	47890 / 3
05/11/99	TELECON WITH Dr. Koller, MEDICAL REVIEWER to discuss the regulatory impact should Novartis decide to terminate Protocol B356 at 16 weeks instead of the planned 24 weeks of double blind treatment.	B356				48213 / 1
05/14/99	Provided updated Chemistry, Manufacturing and Controls information in support of Protocol B351. Included Manufacturing formula and method of preparation, sites of manufacture, packaging and control, Starlix 180 mg tablet, KN 3744844.001.B, dated 12-May-1999.	B351			133	48214 / 1
05/17/99	TELECON FROM FDA Medical Reviewer providing comments on Protocol 103 Amendment 1 submitted 5/10/99. Novartis responded to FDA's comments via voice mail.	103				48217 / 1
6/17/99	Submitted new Protocol No. 0121 entitled; A double-blind, three period, crossover study to evaluate daily glycermic porfiles after 6 weeks of DJN608, repaglinide and placebo treatment in type 2 diabetics.	0121			134	48719 / 1

DATE	DESCRIPTION	SERIAL NO.	PROTOCOL	SUBMISSION TYPE
47,235	Starlix			
09/07/99	Annual Report covering the period from 7-Feb-98 through 6-Feb-99. Includes Clinical and Preclinical information, also an updated Investigator's Brochure.	137		Annual Report
08/13/99	As agreed during the pre-NDA meeting held on 19-Jan-99, Novartis requested a waiver of the requirement for an Environmental Assessment prior to filing the Starlix NDA. Included is the following document: Starlix (DJN608), request for waiver from requirement to prepare an Environmental Assessment, dated August 10, 1999.	136		CMC Amendment
08/03/99	Correspondence which provides a proposal and justification for an improved dissolution method for Starlix tablets which will be included in the NDA submissioin planned for December 1999. The following document is included, DJN608 Starlix (nateglinide) Tablets, proposal for improved dissolution method, dated June 6, 1999.	135		CMC Amendment
06/29/99	TELECON FROM THE FDA medical review officer with comments on the design of Protocol 0121 and B351-E-02, June 17, 1999 amendment.			Memo of Record (telephone report)
06/17/99	Also submitted the following new investigators to Protocol 103; Edward H. Frost, MD; David G. Mulholland, MD; Michael L. Reeves, MD; Sherwyn L. Schawartz, MD.	134	103	New Investigator
06/17/99	Also submitted change in Protocol DNJ 608 B351-E-02; Amendment 4 entitled; Protocol B351E00 filed on 7/17/97 was a 24 week trial. It was amended on 1/23/98 to add B351E01 a 28 week extension at a dose of 120 mg nateglinide. It is being amended to add B351E02, which increases the dose to 180 mg nateglinide. The purpose is to obtain additional long term data at this dose. Also added Dr. David Lackner, principal investigator and deleted principal investigator Dr. Urbanski.	134	B351	New Investigator Other
06/17/99	Also submitted Amendment 6 to Protocol 356 entitled; this trial is being terminated early on June 30, 1999 for administrative reasons. Patients may enter protocol B356-E-01, evtension trial, if eligible to do so. See attached amendment.	134	356	CMC Amendment
06/17/99	Also submitted and deleted several principal investigators in Protocol 356.	134	356	New Investigator
06/17/99	Submitted new Protocol No. 0121 entitled; A double-blind, three period, crossover study to evaluate daily glycermic porfiles after 6 weeks of DJN608, repaglinide and placebo treatment in type 2 diabetics.	134	0121	New Protocol
06/17/99	Also submitted the following new investigators to Protocol 116; Ramon Ramirez, MD; Stasia Louise Miaskiewicz, MD. Also deleted Principal investigator Anthony Fiorillo, MD.	134	116	New Investigator
06/17/99	Also submitted a Response To FDA Inquiry to Protocol 103, regarding the telephone request form Dr. E. Koller, HFD-510 on May 18, 1999.	134	103	Other
06/17/99	Also submitted the following new investigator to Protocol 0121; Leonard M. Keilson, MD.	134	0121	New Investigator
06/07/99	TELECON TO FDA seeking clarification of the procedures for submitting a waiver request for the Environmental Analysis of the Starlix NDA. Also discussed were the stability amendment dated 12/7/98 and the Starlix tradename proposed in the 1/5/99 amendment. Both are acceptable and the decisions for both will be provided in an official letter.			Memo of Record (telephone report)

DATE	DESCRIPTION	SERIAL NO.	PROTOCOL	SUBMISSION TYPE
47,235	Starlix			
11/29/99	In response to FDA request for additional information, provided follow-up to two IND 15 day safety reports (ser # 145 and 146), case nos J/99/00468/DJN and J/99/00572, both of which originated in Japan.	148		Safety Report
11/19/99	FDA FAX which included questions in reference to case # J/99/00582/DJN submitted November 5, 1999.			
11/16/99	TELECON FROM FDA inquiring whether the patient identified under case # J/99/00468/DJN was rechallenged.			Memo of Record (telephone report)
11/08/99	[Japan]; pancytopenia, abdominal pain, nausea, tongue disorder, pharyngitis, follow-up.	147		Safety Report
11/05/99	[Japan]; Dissem. Intravasc. coagulation, jaundice, hepatic function abnormal.	146		Safety Report
11/04/99	[Japan]; jaundice, biliary tract disorder Nos, bilirubinaemia.	145		Safety Report
11/01/99	[Japan]; depression aggravated, suicide attempt, death, follow-up.	144		Safety Report
10/27/99	[Japan]; hypokalaemia, cerebrovascular disorder.	143		Safety Report
10/22/99	[Japan]; anaemia, leucopenia, Vi-Th nerve paralysis.	142		Safety Report
10/11/99	[Japan]; fibrillation atrial, palpitation, follow-up.	141		Safety Report
10/08/99	[Japan]; depression aggravated, suicide attempt, death.	140		Safety Report
10/04/99	Faxed correspondence in follow-up to a voice mail message regarding a post marketing adverse event in Japan. Included is a Medwatch report, Mfr. No. J/99/00467/DJN describing the adverse experience which includes depression aggravated, death, suicide attempt. An official IND safety report will follow.			Safety Report
10/04/99	This submission includes section F (the CMC section) of the IND Annual Report dated 9/7/99. It also includes Protocol CDJN 608 0103, Amendment 2 and new investigator Sam Miller, MD.	139	103	Change In Protocol CMC Amendment New Investigator
10/04/99	The 10/4/99 submission also includes Protocol B351, Amendment 5 and Protocol 364, Amendment 2.	139	B351/364	Change In Protocol
10/04/99	The 10/4/99 submission also includes the following investigators for Protocol CDJN 608 0116: Drs. Guillermo Burlando, Luis DeLoredo, Lisandro Garcia, Ramon Herrera, Mauricio Jadzinsky, Leon Litwak, Isaac Sinay, Gloria Vines, Jorge Waitman.	139	0116	New Investigator
10/04/99	The 10/4/99 submission also includes new investigator E. Walter Hood, MD and revised filing documents for Drs. Kathleen Baskett, Sidney Jones, Thomas O'Barr and Robert Rosen, Protocol B351 investigators. Additional research facilities are also included for Drs. Adrian Dobs and Jeffrey Morton, Protocol B356 investigators.	139	B351/B356	New Investigator
10/01/99	[Japan]; fibrillation atrial, palpitation.	138		Safety Report
09/24/99	TELECON TO THE FDA chemist regarding the review status of the EA waver request dated 8/13/99. The agency indicated that an environmental assessment should be provided with the Starlix NDA. Novartis will start working towards a full EA preparation to meet the December 20, 1999 NDA filing date for Starlix.			Memo of Record (telephone report)

REF	PRODUCT	DATE	DESCRIPTION	SERIAL	PROTOCOL	SUBMISSION TYPE
47,235	Starlix	03/24/2000	[Japan] Reporter unknown; Coma diabetic, creatine phosphokinase increased, muscle necrosis, anorexia, stupor, hyperventilation, fever. Follow-up # 1.	162		Safety Report
47,235	Starlix	03/21/2000	[Japan] Unknown reporter; pneumonia, respiratory insufficiency, dyspnoea, leucopenia.	161		Safety Report
47,235	Starlix	03/21/2000	[Japan] Unknown reporter; amenorrhea.	160		Safety Report
47,235	Starlix	03/17/2000	FDA FAX requesting additional information for case no. J/00/00022/DJN submitted February 8, 2000 .			
47,235	Starlix	03/16/2000	[Japan] Unknown reporter; coma diabetic, creatine phosphokinase increased, muscle necrosis, anorexia, stupor, hyperventilation, fever.	159		Safety Report
47,235	Starlix	03/16/2000	[Japan] Unknown reporter; AV block, follow-up # 1.	158		Safety Report
47,235	Starlix	03/08/2000	TELECON TO the FDA Medical Reviewer reporting a life threatening adverse event reported to Novartis via a Medwatch report from Japan , Case No. J00/00042/DJN. This report describes the following adverse experience: coma diabetic, creatinine phosphokinase increased, muscle necrosis, anorexia, stupor, hyperventilation, fever.			Memo of Record (telepho report) Safety Report
47,235	Starlix	03/06/2000	[Japan]; AV block.	157		Safety Report
47,235	Starlix	02/23/2000	[Japan]: Thrombocytopenia.	156		Safety Report
47,235	Starlix	02/22/2000	Amendment no. 3 to Protocol 0103 and Amendment no. 2 to Protocol 0126. Also provided for Harold K. Cathcart, MD, Protocol 0103 investigator.	155	0103 0126	Change In Protocol New Investigator
47,235	Starlix	02/08/2000	[Japan]; vertigo, micturition frequency.	154		Safety Report
47,235	Starlix	02/07/2000	TELECON FROM the FDA Medical Reviewer requesting that the Excel spreadsheet which accompanied the NDA be provided to her on diskette. The Medical Reviewer also requested that the variables and time points, which she specified to DRA via Fax, be included in the spreadsheet. She wanted this information for Protocols B202, B305, B302 and B355. Novartis may provide this information one protocol at a time starting with Protocol B202.			Memo of Record (telepho report)
47,235	Starlix	02/02/2000	Amendment which provides an updated specifications and control procedures document for Starlix Tablets, Version L. The document was updated to align the clinical specifications and control procedures with the proposed marketed testing monograph.	153		CMC Amendment
47,235	Starlix	01/13/2000	Amendment 1 to Protocol 0126. Also provided for Jon A. LeLevier, MD and Harold K. Cathcart, MD, new investigators for Protocol 0103.	152	0126/ 0103	New Investigator
47,235	Starlix	12/10/99	[Japan]; dissem. intravasc. coagulation, jaundice, hepatic function abnormal, follow-up.	151		Safety Report
47,235	Starlix	12/10/99	[Japan]; jaundice, biliary tract disorder nos, bilirubninaemia, follow-up.	150		Safety Report
47,235	Starlix	12/07/99	Submitted the Protocol CDJN 608 0126 entitled; A randomized, double-blind, five-period, crossover study to evaluate the pharmacodynamics and pharmacokinetics of DJN 608 (nateglinide), repaglinide, and placebo administered with a meal in subjects with mild type 2 diabetes. Also provided for the following new investigator Steven E. Kahn, M. B., Ch.B.	149	0126	New Protocol
47,235	Starlix	12/07/99	Cont'd - Also provided for new investigator Luigi Meneghini, MD.	149	103	New Investigator

NDA PERIOD

REF	PRODUCT NAME	DATE	DESCRIPTION	SUPPLE NO.	TYPE
21-204	Starlix®	03/09/2000	Request to schedule a 90-day conference with the Division. Included is background information to support the meeting request in accordance with the FDA's guidance document for formal meetings with sponsors and applicants for PDUFA products.		Request for FDA
21-204	Starlix®	02/29/2000	FAX TO FDA providing the location of the investigator list and site enrollment information for Protocol B355 in response to FDA request dated February 26, 2000.		
21-204	Starlix®	02/26/2000	FAX FROM FDA requesting location information on investigator list and patient enrollment for Protocol B355.		
21-204	Starlix®	02/23/2000	In response to FDA request, provided via Fed Ex the names and addresses of US and outside of US investigators for Starlix pivotal trials B302, B351 and B354 and table providing the number of patients randomized and completed and the number of SAEs per site for the above trials.		
21-204	Starlix®	02/16/2000	In follow-up to a request from FDA for assistance in locating information on patient enrollment by center in the Starlix clinical trials section in the NDA, Novartis faxed the requested information in a table format.		
21-204	Starlix®	02/16/2000	TELECON WITH FDA requested by Novartis to discuss the firm's recommendation for priority review included in the NDA cover letter. The agency indicated that they would not grant priority review to the NDA , nor would they promise a 10-month standard review. FDA believes that Novartis has not met the criteria for priority review. Additionally, the FDA Project Manager commented on the NDA index indicating that it could be clearer.		Memo of Record report)
21-204	Starlix®	02/11/2000	TELECON FROM the FDA Project Manager informing Novartis that the NDA is acceptable for filing, but that it will be designated for standard review, since the review team concluded that it does not warrant priority review. Also, an Advisory Committee meeting will not be needed. Novartis requested a meeting with the Acting Division Director to discuss the review priority for the NDA.		Memo of Record report)
21-204	Starlix®	01/31/2000	In follow-up to a January 24, 2000 teleconference with the FDA , Novartis provided a replacement page for page 44 in volume 2 of the original NDA. The referenced page contains packaging configuration information for each tablet strength.		CMC
21-204	Starlix®	12/27/99	TELECON FROM the FDA Document Room with a question regarding the tape that accompanied the NDA. Novartis informed the agency that the tape is the official copy.		Memo of Record report)
21-204	Starlix®	12/21/99	FDA LETTER acknowledging receipt of the original NDA submitted on December 17, 1999. Assigned NDA no. 21-204.		
21-204	Starlix®	12/17/99	Original NDA for Starlix tablets for the treatment of Type 2 diabetes mellitus. Included are the following CMC documents: Description of pharmaceutical form and composition, manufacturing formula and method of preparation, Nateglinide 60mg, 120mg, 180mg film-coated tablets, Novartis No.: KN 3741287.00.0017.J/018.J; KN 3742038.00.010.C/011.C; KN 3744844.00.009.C/010.C, respectively, dated 1-Nov-1999. Also included Registration Stability Report, Nateglinide 60, 120, 180 mg tablets, Report RSR6005B, dated 14-Dec-1999. Complete submission in 312 vols.		Original NDA
21-204	Starlix®	10/08/99	Letter from Novartis thanking the FDA for providing assistance in assigning NDA number 21-204 for the upcoming NDA for Starlix.		

REF	PRODUCT NAME	DATE	DESCRIPTION	SUPPLE NO.	TYPE
21-204	Starlix®	05/12/2000	In partial response to the telefax dated April 11, 2000 from the statistical reviewer, provided copies of protocols and amendments for Studies B202, B302, B304 and B354. Protocols, B351, B252, B355 will be submitted in a follow-up correspondence.		Clinical
21-204	Starlix®	05/04/2000	At the request of the Pharmacology Reviewer, provided data from carcinogenicity studies and dose finding studies in electronic format.		Preclinical
21-204	Starlix®	04/20/2000	Replacement copy of the spreadsheet of glycemic data from Protocol B355 on diskette. This submission completes Novartis' fulfillment of FDA's request for replacement spreadsheets.		
21-204	Starlix®	04/18/2000	Submitted the 4-month (120 day) safety update report for pending NDA 21-204. The submission includes data tabulations in electronic format from completed clinical trials, Protocol B356-E-01 and 102. Complete submission in 12 vols.		
21-204	Starlix®	04/11/2000	FDA FAX from Joy Mele, FDA statistician, requesting additional information for Starlix studies as listed.		
21-204	Starlix®	04/10/2000	At the request of the biopharmaceutics reviewer, provided data and information from sections 6 and 8 of the NDA regarding Protocols W251, W351, W353, W366 in electronic format.		Clinical
21-204	Starlix®	03/31/2000	TELECON FROM the FDA Pharmacologist with questions regarding the 2 year mouse carcinogenicity study (Report 94/0143 and whether the firm was planning to submit electronic datasets for the study. The IPT representative from PCS who joined the discussion agreed to make arrangements to provide the requested data electronically for the rat and mouse studies. Pathology data or tumor tapes are also being prepared for submission.		Memo of Record report) Preclinical
21-204	Starlix®	03/31/2000	Provided a replacement copy of the spreadsheet of glycemic data from Protocol B351 in electronic format.		Clinical
21-204	Starlix®	03/30/2000	Provided a pediatric plan and request for partial waiver for the study of Starlix in pediatric patients with Type 2 diabetes below the age of 10.		Clinical
21-204	Starlix®	03/24/2000	Provided the FDA with the modified spreadsheet of glycemic data from Protocol B302 in electronic format. Novartis is in the process of making the requested modifications for Protocols B351 and B355.		Clinical
21-204	Starlix®	03/21/2000	Correspondence requesting feedback from the agency on the Starlix tradename for the product which the agency is evaluating as part of the NDA review. Reference is also made to Novartis' March 9, 2000 request for a 90-day conference which could not be scheduled at this time as the review has not been advanced sufficiently. A request will be made later for a meeting when the review has advanced sufficiently.		
21-204	Starlix®	03/20/2000	TELECON to the FDA chemistry reviewer to inquire about the status of the Starlix tradename. Although Novartis was instructed by the project manager to contact the chemistry reviewer for an update of the tradename, the responsibilities for this phase of the review are not clear at the present time. Novartis will follow-up with the project manager to expedite the review.		Memo of Record report)
21-204	Starlix®	03/17/2000	Provided modified spreadsheet of glycemic data from Protocol B202.		
21-204	Starlix®	03/13/2000	TELECON WITH FDA to receive details of the NDA Biopharm Reviewer's expectation regarding format and content for electronic datasets for Protocols W251, W351, W353 and W366. Novartis' proposal to provide the datasets for the referenced studies by the end of March was accepted.		Memo of Record report)

REF	PRODUCT NAME	DATE	DESCRIPTION	SUPPLE NO.	TYPE
21-204	Starlix®	07/17/2000	Replacement copy (electronic) of the Excel spreadsheet for Protocol B351. This is a replacement copy of the file that was provided initially in the March 31, 2000 amendment.		Clinical
21-204	Starlix®	07/14/2000	Replacement copies of the SAS data files for Protocols B302 and B351 on CD ROM. .		Clinical
21-204	Starlix®	07/06/2000	In response to the Statistical Reviewer's telefax request dated June 19, 2000 provided replacement copies of the SAS data files for Protocols B251, B252, B351 and B354 on CD ROM. Also provided patient disposition information in hard copy as requested.		Clinical
21-204	Starlix®	06/28/2000	Provided replacement copies of the SAS data files for Protocols B202, B302, B304 on CD ROM. This is a follow-up to the June 21, amendment and includes the variable "Duration of Diabetes (Years)" as requested by the FDA Statistician via telephone on June 23, 2000.		Clinical
21-204	Starlix®	06/21/2000	Replacement copies of the SAS data files for Protocols B202, B302 and B304 on CD ROM, submitted in response to a request from the FDA Statistician received via telefax dated May 26, 2000 (copy attached). Also included is patient disposition information regarding the three protocols provided in hard copy as requested.		Clinical
21-204	Starlix®	06/19/2000	FAX FROM FDA requesting SAS datasets for Studies B251, B252, B351 and B354 and additional patient disposition tables containing specific information as listed.		Clinical
21-204	Starlix®	06/12/2000	TELECON FROM the FDA Statistician indicating that the June 9, 2000 amendment consisting of reformatted files relating to B202 are satisfactory with the exception of minor preferences as outlined. FDA requested that the SAS datasets for the three trials (B202, B302 and B304) be submitted on a CD ROM and the other information as hard copy.		Memo of Record report)
21-204	Starlix®	06/09/2000	Replacement copy of the SAS data files and summary tables on dropouts in Protocol B202 on diskette, submitted as a partial response to the FDA Statistician's request dated May 26, 2000.		Clinical
21-204	Starlix®	06/05/2000	As requested by the FDA Pharmacologist in a June 1, 2000 telephone conversation, provided carcinogenicity information contained in the study entitled, "Calculations of safety factors and human equivalent doses derived from rat carcinogenicity studies, dated June 1, 2000.		Preclinical
21-204	Starlix®	06/02/2000	FAX to FDA which includes information regarding safety factors for the carcinogenicity studies in rats as requested in the June 1, 2000 telephone request. This information will be officially submitted to the NDA as an amendment.		Preclinical
21-204	Starlix®	06/01/2000	At the request of the statistical reviewer dated April 11, 2000, Novartis provided copies of Protocols B251, B252, B351 and B356 including all amendments.		Clinical
21-204	Starlix®	06/01/2000	TELECON FROM THE FDA Pharmacologist requesting additional information on the doses used in the rat carcinogenicity studies compared to human equivalent doses.		Memo of Record report)
21-204	Starlix®	05/31/2000	TELECON FROM the FDA Statistician requesting new SAS datasets for Protocols B202, B302, B304 reformatted in accordance with specifications as outlined.		Memo of Record report)
21-204	Starlix®	05/15/2000	TELECON FROM THE FDA Pharmacologist with questions regarding the toxicology section of the NDA. A conference call was arranged by DRA with Dr. Smith from PCS to provide response to the FDA's questions.		Memo of Record report)

REF	PRODUCT NAME	DATE	DESCRIPTION	SUPPLE NO.	TYPE
21-204	Starlix®	10/13/2000	TELECON FROM FDA, providing feedback on some of the tables Novartis submitted in response to the 16 item request which FDA sent on September 12, 2000.		Memo of Record report)
21-204	Starlix®	10/13/2000	In response to FDA's faxed request for additional clinical information received on September 12, 2000, provided response to items 5 and 6 listed in the fax. This completes Novartis' response to all 16 items in FDA's request. Additionally, Novartis indicated that information will be provided as discussed in the October 13, 2000 teleconference.		Clinical
21-204	Starlix®	10/10/2000	In response to FDA request for additional clinical information received via telefax on September 12, 2000, provided information to address items 7 through 9. Partial response to the FDA request was provided on September 21 and October 4, 2000. Reponse to items 5 and 6 will be submitted in approximately one week when the requested information is assembled.		Clinical
21-204	Starlix®	10/04/2000	Provided information and documentation addressing FDA 's questions listed in the September 12, 2000 telefax. Information in response to items 5 through 9 requested in the telefax will be provided in approximately one week. Submission in 3 vols.		Clinical
21-204	Starlix®	09/21/2000	In accordance with a telephone request from the Division communicated on September 12, 2000, Novartis provided electronic datasets for Protocols B251 and B351 on diskette.		Clinical
21-204	Starlix®	09/19/2000	Request to import bulk drug product, Starlix Tablets, for the purpose of analytical testing and packaging of bulk tablets in anticipation of FDA approval of NDA 21-204 on 17-Dec-2000.		
21-204	Starlix®	09/13/2000	Provided draft labeling updated with new information regarding glycemic effects by prior treatment (naive vs previously treated).		Labeling
21-204	Starlix®	09/12/2000	FDA FAX requesting clarification on a number of items regarding the NDA as outlined.		
21-204	Starlix®	09/06/2000	In response to a 29-Aug-00 telephone request from the FDA Project Manager, provided draft labeling, including artwork, for the immediate bottle container (trade and sample) and for the carton of the sample bottle container.		CMC
21-204	Starlix®	08/17/2000	In follow-up to a telephone conversation regarding the FDA review clock for the NDA, provided Sharon Olmstead , DRA Washington Liaison, copy of FDA's minutes of the February 16, 2000 teleconference with the agency to discuss FDA's decision to assign a standard review for the Starlix NDA.		
21-204	Starlix®	08/15/2000	FDA FAX denying Novartis' March 30, 2000 proposed pediatric study request. The FDA determined that there is not enough information currently available to adequately issue a Written Request.		
21-204	Starlix®	08/14/2000	TELECON WITH FDA to get an update from the CSO and the medical reviewer regarding review of the NDA. The review team cannot meet the originally targeted 10 month cycle (reasons outlined) and has decided to revert to the 12 month review cycle. Labeling issues were also discussed.		Memo of Record report)
21-204	Starlix®	08/03/2000	Submitted the following Stability Report: DJN608 (Nateglinide, Starlix) 60, 120 and 180 mg tablets - Registration Stability Report, RSR6005C.01, dated July 26, 2000.		CMC
21-204	Starlix®	08/02/2000	As requested by the FDA in the July 31, 2000 telephone conversation, provided amendment to the Environmental Assessment to include additional information on the microbial inhibition test, section 6.5.1 in the original EA. A faxed copy of this amendment is also forwarded to Nancy Sager, EA Reviewer.		CMC
21-204	Starlix®	07/31/2000	TELECON FROM FDA requesting more complete information in section 6.5.1 (microbial inhibition test) of the original Environmental Assessment.		CMC Memo of Record report)

REF	PRODUCT NAME	DATE	DESCRIPTION	SUPPLE NO.	TYPE
21-204	Starlix®	11/27/2000	FDA FAX which contains revised Table 2 under "combination with metformin" relating to the Starlix package insert.		Labeling
21-204	Starlix®	11/22/2000	FDA FAX providing comments relating to the package insert labeling for Starlix. These comments are preliminary and subject to change as the agency finalizes their review of the application.		Labeling
21-204	Starlix®	11/21/2000	FDA FAX providing OPDRA recommendations for labeling revisions that might minimize potential medication errors that could occur with users of the product. These comments do not reflect a final decision. They are provided in order to give the sponsor preliminary notice of issues that have been identified.		Labeling
21-204	Starlix®	11/17/2000	FDA LETTER indicating that, in response to Novartis' September 9, 2000 request to import bulk drug product Starlix tablets, in anticipation of FDA approval of the NDA, the agency has no objection to this importation.		
21-204	Starlix®	11/09/2000	TELECON TO FDA to follow-up on the telephone conversation dated November 7, 2000 regarding the Starlix tradename. The Office of Postmarketing Drug Risk Assessment indicated that they completed their review and sent their report to the project manager. The reviewing officer indicated that the tradename is not an issue, but that there might be recommendations for some minor changes to the bottle label.		Memo of Record report)
21-204	Starlix®	11/07/2000	FDA FAX providing pharmacology/toxicology review comments relating to the package insert labeling of the original NDA submitted December 17, 1999.		Labeling
21-204	Starlix®	11/07/2000	TELECON TO FDA (11/1/00) inquiring about the review status of the draft labeling, including artwork, submitted on September 6, 2000. The reviewing chemist indicated that no additional information is requested regarding the CMC section of the NDA. On November 7, 2000 Novartis contacted the Project Manager regarding the status of the tradename review and was informed that OPDRA is reviewing the tradename.		Labeling Memo of Record report)
21-204	Starlix®	11/06/2000	In response to a telephone request on November 2, 2000, provided table which lists the individual dissolution test results for 12 tablets for batch H-05226. This table is an addendum to the report submitted on October 20, 2000.		
21-204	Starlix®	11/06/2000	TELECON FROM FDA requesting immediate feedback on the financial disclosure location in the NDA and information on reference ranges for fructosamine and HbA1c used for the clinical studies. Novartis provided response to FDA's questions right away.		Memo of Record report)
21-204	Starlix®	11/02/2000	TELECON FROM the FDA requesting information on phase 3 formulations, dose proportionality data and dissolution data. Novartis contacted the biopharm reviewer on November 2, 2000 to provide information in response to items 2 and 3 of the FDA request.		CMC Memo of Record report)
21-204	Starlix®	11/01/2000	In response to a telephone request from the FDA Medical Reviewer, the following information is provided: Post text table 10.1-2a for phase 2 trials B202 and B251, core and extension; Table 3 (number of patients with AEs and Table 3a (number of patients with hypoglycemia symptoms); diskette for Protocol B355 which includes both glycemic and insulin data for each patient.		Clinical
21-204	Starlix®	10/23/2000	In response to a telephone request from the Medical Reviewer received on October 13, 2000, provided reformatted Post Text Tables 10.102, Table 3 and 3a for trials B302, B304, B351, B351E01, B354, B355 and B356.		Clinical
21-204	Starlix®	10/20/2000	In response to a telephone request from the biopharmaceutics reviewer, provided report entitled, "Nateglinide, 60 mg, 120 mg, 180 mg tablets, Dissolution performance individual data, dated 18-Oct-2000.		CMC
21-204	Starlix®	10/18/2000	FAX to FDA providing NDA location references for insulin results by treatment group, Protocol B355. This information is provided in follow-up to the teleconference dated October 18, 2000 discussing the calculation of glucose AUC in Protocol B355.		Clinical
21-204	Starlix®	10/16/2000	Addendum to the October 13, 2000 telephone report to amend the information in the telephone report to address the phase 2 studies.		Memo of Recor report)

REF	PRODUCT NAME	DATE	DESCRIPTION	SUPPLE NO.	TYPE
21-204	Starlix®	12/20/2000	FAX to FDA providing the current working copy of the Starlix package insert.		Labeling
21-204	Starlix®	12/20/2000	In reference to FDA request to delete the sentence in the Metformin paragraph in the package insert regarding HbA1c, Novartis concluded that there is adequate data to support the legitimacy of the statement and provided arguments to support its conclusion.		Labeling
21-204	Starlix®	12/19/2000	At the request of the FDA, Novartis clarified the nature and extent of the supplementary safety update for Starlix submitted on December 13, 2000.		
21-204	Starlix®	12/19/2000	Response to FDA's Discipline Review Letter dated December 18, 2000, which included questions regarding information contained in the NDA safety updates submitted on April 18 and December 13, 2000.		
21-204	Starlix®	12/18/2000	In response to FDA recommendations on container and carton labels included in the November 21, 2000 FDA fax, Novartis agrees to delete the picture of the man next to the proprietary name on the carton. However, the firm proposes not to revise the statement of strength as recommended. This was communicated to the project manager via telephone on 11/22/00 and it is believed that it was accepted.		Labeling
21-204	Starlix®	12/18/2000	FDA DISCIPLINE REVIEW LETTER indicating that the agency has reviewed the safety updates dated April 18 and December 13, 2000 and identified deficiencies as outlined.		
21-204	Starlix®	12/18/2000	Amendment to the pending NDA with response to two dissolution questions included in FDA fax dated December 15, 2000. This response was faxed to the Division of Biopharmaceutics on December 15, 2000 and FDA informed Novartis at the end of the day that the proposal as presented in the fax, has been accepted.		CMC
21-204	Starlix®	12/15/2000	Provided, via facsimile, response to the two dissolution questions listed in FDA's fax dated December 14, 2000.		CMC
21-204	Starlix®	12/14/2000	FDA FAX providing comments relating to the dissolution profile from the review of the clinical and biopharmaceutical sections of the NDA.		Labeling
21-204	Starlix®	12/13/2000	In response to a verbal request, provided a supplementary safety update.		
21-204	Starlix®	12/13/2000	As requested, provided an additional desk copy (12 volumes) of the 120-Day safety update.		
21-204	Starlix®	12/13/2000	FDA FAX providing labeling comments for Starlix.		
21-204	Starlix®	12/11/2000	Submitted revised annotated proposed labeling dated 12/7/00.		Labeling
21-204	Starlix®	12/08/2000	FAX to FDA providing copies of labeling sections from other approved products that treat diabetes which are relevant to Novartis' ongoing discussions concerning labeling for Starlix. Additionally, included are the minutes of the FDA End-of-Phase 2 meeting describing agreement on the use in the PI of prandial glucose and insulin levels.		
21-204	Starlix®	12/08/2000	FAX TO FDA providing the dosing rationale requested by the agency earlier in the week. Additionally, a separate fax is being submitted to the NDA on this date which provides supporting documentation for the teleconference that took place on December 8, 2000.		
21-204	Starlix®	12/07/2000	FDA FAX providing labeling comments for Starlix NDA 21-204.		Labeling
21-204	Starlix®	12/01/2000	Submitted revised version of draft labeling which includes Novartis' original draft, the comments provided by FDA and counter proposals in response to FDA revisions. Novartis is willing to meet with the agency to resolve any issues that may remain after review of the re-drafted text.		Labeling

REF	PRODUCT NAME	DATE	DESCRIPTION	SUPPLE NO.	TYPE
21-204	Starlix®	12/22/2000	FDA APPROVAL LETTER for NDA 21-204 which provides for the use of Starlix as monotherapy as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. Additionally it provides for the use of Starlix concomitantly with metformin to improve glycemic control. Requested is FPL, three copies of introductory promotional materials and one market package of the drug product. Reference is also made to the requirement regarding assessment of safety and effectiveness of the product in pediatric patients.		
21-204	Starlix®	12/22/2000	In response to an FDA concern regarding the statement in the package insert concerning HbA1c reductions, Novartis indicated that the study report for Protocol B351 included an analysis to support the referenced statement.		Labeling
21-204	Starlix®	12/22/2000	FDA FAX which includes language for the Starlix labeling.		Labeling
21-204	Starlix®	12/22/2000	In follow-up to discussions held with the agency regarding the package insert, submitted proposed revision to the statement in the package insert regarding the Starlix combination therapy/Metformin subsection.		Labeling

APPENDIX F

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent Re. 34,878
Issued: March 14, 1995
To: Shigeshi Toyoshima, Yoshiko Seto, Hisashi Shinkai, Koji Toi and Izumi Kamashiro
For: HYPOGLYCEMIC AGENT

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 CFR §1.740(b)

Sir:

The undersigned Official of Ajinomoto Co., Inc., the Owner of U.S. Patent No. Re. 34,878 for which the instant Application for Extension of Patent Term under 35 USC §156 is submitted, hereby declares as follows:

1. That he is an Official of Ajinomoto Co., Inc., and has the power to obligate the Corporation and further has general authority from Ajinomoto Co., Inc. to act on its behalf in patent matters;

2. That he has reviewed and understands the contents of the application being submitted pursuant to 35 USC §156 and 37 CFR §1.740;

3. That he believes the patent is subject to extension pursuant to 35 USC §156 and 37 CFR §1.710;

4. That he believes an extension of the length of time claimed is justified under 35 USC §156 and the applicable regulations;

5. That he believes the patent for which extension is sought meets the conditions for extension of the term of a patent as set forth in 37 CFR §1.720.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this Application, the Patent, and my registration resulting therefrom.

Signed this 8th day of February, 2001.

Tetsuo Kono
General Manager
Intellectual Property Department